# PROGRESS

...IN...

# Alkaloidal Chemistry

DURING THE YEAR 1904.

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...BY...

H. M. GORDIN.



MILWAUKEE,
Pharmaceutical Review Publishing Co.
1905.

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# Progress in Alkaloidal Chemistry During the Year 1904.

By *H. M. Gordin.*

The chemistry of alkaloids has received many valuable contributions during the year of 1904. While the year's work cannot show such important syntheses as those of atropine and nicotine, accomplished during the preceeding year, many investigations of great importance fall to the credit of last year. The constitution of some alkaloids, for example, that of ricinine, has been completely established. The researches of Knorr and others upon the constitution of morphine are bringing this important problem very near to its solution. The relations between the other opium alkaloids and the constitution of some of them, e. g., apomorphine are also being cleared up. The constitution of conhydrine and of the different coniceines also promises to be very soon worked out. The identity of lupinidine with sparteine was shown by Willstädter and his collaborators. Papaverine and cotarnine received a great deal of attention last year and many interesting derivatives of these bases were prepared by various investigators. New color reactions for the indentification of some alkaloids were discovered by Reichard and others and the presence or absence of certain alkaloids in certain plants was also definitely established. Only one new alkaloid, skimmianine, was discovered during 1904.

I shall now take up in alphabetical order all those alkaloids the chemistry of which was investigated during 1904 beginning with two investigations on some general properties of the vegetable bases.

**Alkaloids.** Their influence upon certain reactions of oxidation. K. Feder has investigated the influence exerted by alkaloids upon certain reactions of oxidation. Schlagdenhaufen and Schaer had already shown that while an aqueous solution of mercuric chloride had no effect whatever upon tincture of guaiac, the addition of even a trace of a free alkaloid to the mixture of the tincture and the mercury salt produces a blue color. In the present investigation it is shown that most alkaloids are capable of inducing oxidations in mixtures of cupric, ferric, mercuric, silver, gold and platinum salts

with many oxidizable substances, like pyrogallol, tincture of guajac, aloin, pyrocatechin, hydroquinone and orcin, — all of which in the absence of alkaloids are either not affected at all or affected only very slightly by the above mentioned salts.

On the other hand the influence of alkaloids upon the oxidation of glucose by copper and mercury salts is only very slight.

The same is true with regard to the biuret reaction of albumenoids.

In the course of this investigation it was found that the unfavorable influence which the presence of glucose exerts upon the biuret reaction can be eliminated by the addition of a little hydrogen peroxide. Arch. d. Pharm., 1904, p. 680.

**Ammonium bases of alkaloids.** M. Scholtz and K. Bode find that on combining the various N-alkyl coniines or N-alkyl conhydrines with alkylhalides there are always formed two optical isomers when the five radicles attached to the nitrogen atoms are different from each other. These isomers differ from each other not only in direction and magnitude of rotation but also in solubility, melting point etc. This is as it ought to be expected. Coniine and conhydrine both containing assymetric carbon atoms are themselves optically active. When the nitrogen atoms of these bases through the addition of five different groups also become assymetric there ought to be formed in each case two compounds in which, to one and the same function of the assymetric carbon atom, there ought to be an addition of the dextro effect of the now assymetric nitrogen atom in one case and of the laevo effect in the other case. With + C, for example, we ought to get the following two compounds:

$$\begin{matrix} +C & \text{and} & +C \\ +N & & -N \end{matrix}$$

Such compounds are, therefore, not optical antipodes which differ from each other only in the direction, or in the absolute magnitude of rotation, but really optically different substances in which both the sense and the absolute magnitude of rotation ought to be different. Such isomeric compounds generally have different melting points, different solubilities etc.

As most alkaloids containing assymetric carbon atoms are optically active it ought to be possible to obtain from each of them two optical isomers which, like those obtained from coniine and conhydrine, would differ from each other in several physical properties,

when their nitrogen atoms are made assymetric. But on making experiments with strychnine, brucine, nicotine, tropine, atropine and cinchonine it was found that no such optical isomers were formed.

It would seem, therefore, that the presence of the propyl group in coniine and of the oxypropyl group in conhydrine is particularly favorable to the formation of the above mentioned kind of isomerism. The alkyl derivatives tried in this investigation were: benzylbromide, methyliodo-acetate and benzyl-iodide. Arch. d. Pharm., 1904, p. 568.

**Atropine.** C. Reichard finds that on warming a mixture of atropine sulphate and mercurous nitrate with a few drops of water double decomposition takes place at first with the formation of the difficultly soluble mercurous sulphate. On further heating the mixture becomes black from the reduction of the mercury salt and an agreeable odor is developed due to the action of the liberated sulphuric acid on the atropine.

With silver nitrate, platinum tetrachloride or palladium chloride the same reaction takes place but is not as sharp as with the mercurous nitrate.

On adding some sulphuric acid and bismuth chloride to a strong solution of atropine sulphate a yellow color is developed which disappears on standing or upon addition of water.

With sodium nitroprusside atropine behaves like cocaine (Chem. Ztg. 28, p. 299) with this difference that in the case of atropine an aromatic odor is developed which does not take place with cocaine. Atropine also differs from cocaine in that the former does not give any color reaction with titanic acid and sulphuric acid (loc. cit.).

On adding some hydrochloric acid to a mixture of atropine sulphate and sugar the mixture assumes a rose red color. With very small amounts of the alkaloid the color disappears after a while but reappears again on the application of heat. Alkalies change the color to green.

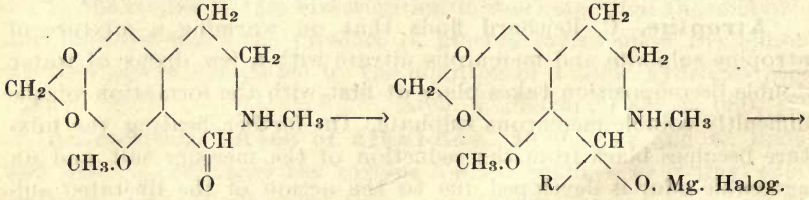
Arsenates and arsenites are reduced by atropine slowly in the cold, quickly on application of heat.

With antimony trichloride atropine gives a green color which is not changed by stannous chloride. (Morphine is colored red by the same reagent.)

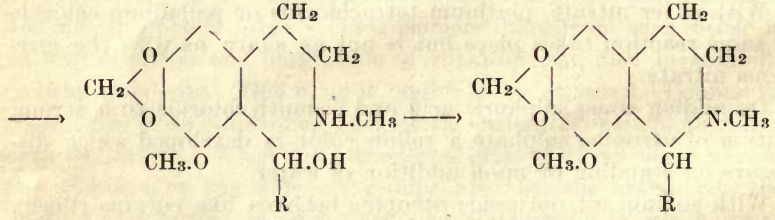
Warmed with a very dilute solution of cobaltous nitrate atropine sulphate gives a green color which is destroyed by ammonia. A drop of strong sodium hydroxide changes the color to violet.

With cobalt sulphate atropine produces an aromatic odor but gives no color reaction. Chem. Ztg., 28, p. 1048.

**Berberine.** M. Freund and H. Beck have prepared some alkyl derivatives of dihydroberberine by means of Grignard's reaction. It has been shown in a previous paper that cotarnine forms alkyl derivatives of hydro-cotarnine when subjected to Grignard's reaction. The reaction with cotarnine takes place according to the following scheme:

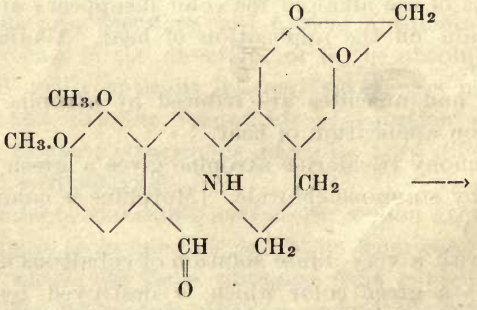



Cotarnine.

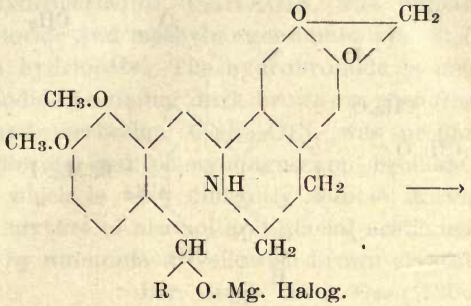


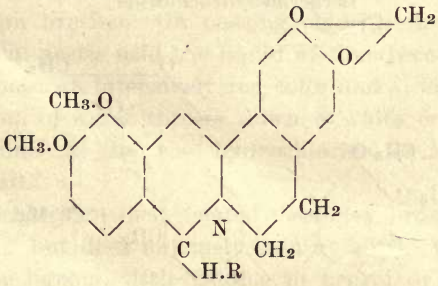

R-hydrocotarnine.

As according to Gadamer (Chem. Ztg. 1902, 291) the constitution of berberinal is similar to that of cotarnine, berberinal ought to react with Grignard's reagent in the same way as cotarnine. Experiments showed that such is really the case. The reaction in the case of berberinal goes according to the same scheme as with cotarnine:



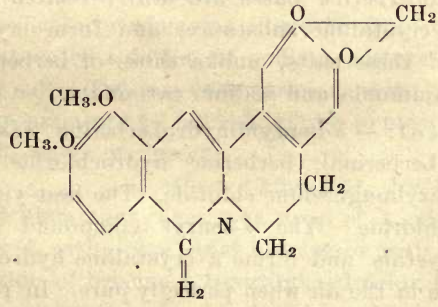

Berberinal.



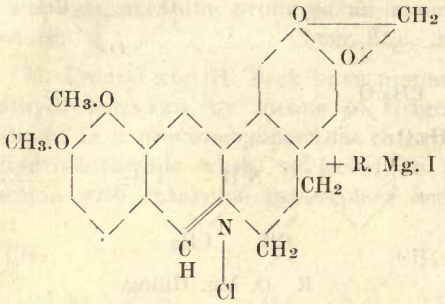

R-Dihydroberberine.

These compounds being derivatives of dihydroberberine are named α-R-dihydroberberines.

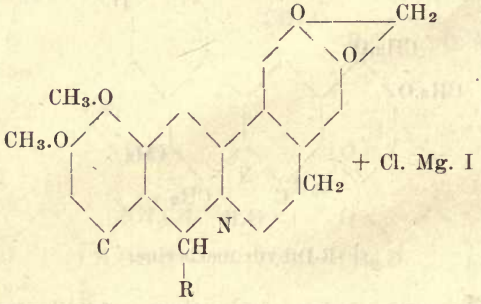



Dihydroberberine.

These α-alkyldihydroberberines can also be prepared by treating berberine salts with Grignard's reagent, for example berberine hydrochloride or berberine cyanide.




Berberinehydrochloride.




α-R-dihydroberberine.

These dihydroberberine bases are nearly related to corydaline. They are yellow crystalline substances and form crystalline salts. The solutions of these salts, unlike those of berberine salts, are precipitated by ammonia and sodium carbonate.

Experimental: — α-Benzyldihydroberberine was prepared by heating either berberinal, berberine hydrochloride or berberine cyanide with benzylmagnesium chloride. The best yield is obtained from the hydrochloride. The α-benzyl compound crystallizes in lemon yellow crystals and forms a crystalline hydrochloride which is perfectly stable in the air when perfectly pure. In presence of impurities the hydrochloride is decomposed on standing and develops the odor of benzoic aldehyde when dissolved in water.

When heated with methyliodide to 100° α-benzyldihydroberberine forms an iodomethylate, $C_{28}H_{28}O_4NI$. It is a crystalline powder difficultly soluble in alcohol.

α-Methyldihydroberberine, $C_{21}H_{21}O_4N$, was prepared from berberine hydrochloride and methylmagnesiumiodide. It forms a hydrobromide and a hydriodide. The hydrobromide is much less stable than the hydriodide becoming dark brown on standing.

α-Phenyldihydroberberine, $C_{26}H_{23}O_4N$, was prepared from berberine hydrochloride and phenylmagnesium bromide. It forms a hydrobromide which is very difficultly soluble in water. From it solutions in a mixture of alcohol and glacial acetic acid the free base is precipitated by ammonia in yellowish brown crystals.

Ber. dtsch. chem. Ges., 1904, p. 4673.

**Brucine.** C. Minunni and R. Ciusa have investigated the action of chlorine upon brucine. On passing chlorine into a solution of brucine in glacial acetic acid the liquid at first becomes yellow, after a while it assumes an intensively red color and at last again becomes yellow. Addition of water throws down a white crystalline powder which was found to be the hydrochloride of hexachlorbrucine, $C_{23}H_{20}O_4N_2Cl_6HCl$.

The hydrochloride when heated becomes brown at 120° and darkens at 200° but does not melt even at 260°. It is insoluble in water, ether or ligroin, little soluble in benzol or chloroform and very easily soluble in alcohol, acetic ether or methyl alcohol. It is also soluble in potassium hydroxide and ammonia. On exposure to light it assumes a rose red color. It dissolves in sulphuric acid with evolution of hydrochloric acid. Strong nitric acid does not color the salt. It is physiologically inactive.

The free hexachlorbrucine was liberated from the hydrochloride by adding a saturated solution of sodium acetate to the alcoholic solution of the salt. The free base forms a white powder which becomes yellow on exposure to light, is soluble in most organic solvents and insoluble in water or ligroin.

Gazz. Chim. Ital., 1904, 11, p. 360.

C. Reichard finds that when one drop of a solution of bismuth chloride is mixed with some solid brucine or with a drop of a concentrated solution of brucine a beautiful red color is developed. On now adding one drop of hydrochloric acid and evaporating to dryness the color becomes more intensely red and does not change to yellow as is the case with the red color obtained from brucine and nitric acid. For the success of the reaction it is necessary that the brucine be always in excess.

If bismuth subnitrate be used in the reaction instead of the chloride there is no color even on warming the mixture but the addition of hydrochloric acid to the mixture produces the red color.

Arsenic and tin salts do not give any color reactions with brucine. Antimony trichloride produces the red color only on application of heat. Mercurous salts do not react at all with brucine. Mercuric salts react only in the heat.

The presense of cadmium, copper and lead do not interfere with the reaction of brucine with bismuth chloride.

Chem. Ztg., 1904, p. 1024.

C. Reichard has examined Flückiger's reaction for brucine (Zeitschr. f. anal. Chem., 1876, pp. 15 and 342) and found that in the absence of free nitric acid free brucine gives no color with mercurous nitrate but if a solution of mercurous nitrate to which some brucine has been added, be kept for some time, there is a reduction of the mercury salt to metallic mercury. With a salt of brucine in dilute solution mercurous nitrate gives at first a yellow color which upon concentration of the liquid is changed to a carmine red. Addition of water to this red liquid brings back the yellow color. On prolonged standing the mercury salt is reduced by the salt of brucine in the same way as by the free alkaloid.

With mercuric nitrate neither the free base nor its salts show any reaction in the cold, but on evaporating a solution containing mercuric nitrate and some brucine a color is produced which is brown-red in artificial light and violet with a yellow contour in daylight. Addition of stannous chloride to this colored residue produces a white curdy precipitate.

Silver nitrate is quickly reduced by brucine. On rubbing together free brucine with some silver nitrate and then moistening the mixture with water black metallic silver soon separates out even in the cold. Application of heat makes the reaction more delicate. When a solution of a brucine salt is mixed with a solution of silver nitrate the liquid is at first colorless but very soon a deposit in the form of a black powder makes its appearance. On evaporating the liquid a varnish-like coating is obtained together with the black powder. This coating is colored deep red by stannous chloride. The red color produced by the stannous chloride cannot be ascribed to the action of the nitric acid which comes from the silver nitrate for the reason that no color is produced by the silver nitrate before the addition

of the stannous chloride. Besides, the red color produced by nitric acid in solutions of brucine is changed to violet by stannous chloride. This red color produced by the stannous chloride does not disappear upon the addition of water and the presence of an excess of hydrochloric acid does not interfere with the reaction.

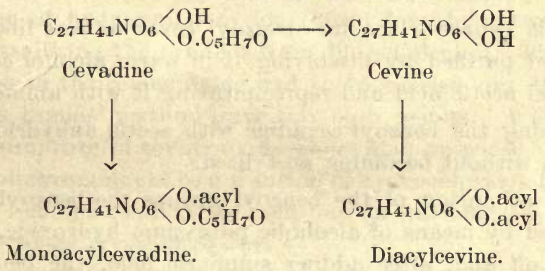
Silver nitrite behaves with brucine exactly like silver nitrate.

On evaporating a solution of copper nitrate with some brucine a violet blue color is produced which gradually changes to dark blue. Addition of stannous chloride to this colored residue changes the color first to red, then to brownish-red and at last to brownish-yellow. On now applying heat the color is changed to deep violet.

When brucine or its sulphate is rubbed up with a drop of a ten per cent solution of formic aldehyde and the moist mixture evaporated to dryness a white residue is left which becomes light blue when touched with a drop of a solution of stannous chloride. The reaction takes place even in the cold. Application of heat changes the color to yellowish-green. Strychnine does not give this color reaction.

Chem. Ztg., 1904, pp. 912.

**Cevadine.** M. Freund finds that it is possible to introduce only one benzoyl or acetyl group into cevadine whereas into cevine two such groups can be introduced. The relation between these two alkaloids can therefore be expressed as foliows:




It was further found that hydrogen peroxide oxidizes cevine very quickly to a substance having the formula $C_{27}H_{43}NO_9$. As this substance can be easily reduced back to cevine by means of sulphur dioxide it must belong to the group of amino oxides, $R_3:N:O$, and can, therefore, be named cevine oxide. As the oxidation of cevine by hydrogen peroxide takes place almost immediately and the cevine oxide crystallizes well and has a sharp melting point, the reaction

can be used for the identification of cevine which crystallizes with difficulty and has no sharp melting point.

From the formation of cevine oxide some conclusions can be drawn with regard to the function of the nitrogen atom in cevine. As only certain tertiary bases are capable of forming amino oxides the nitrogen in this alkaloid must be tertiary. This has already been shown previously by the formation of cevine iodomethylate. As pyridine does not form such an amino oxide it is reasonable to suppose that quinoline and isoquinoline being derivatives of pyridine are also incapable of forming amino oxides; hence the nitrogen atom in cevine cannot belong to a pyridine complex. The bases that are capable of being easily converted into amino oxides all belong to the type $R_2:N.CH_3$, e. g., trimethylamine, N-alkylpiperidenes, N-alkylpyrrolidines and dimethylaniline. As experiment had shown the absence of a $=N.CH_3$ group in cevine it must be supposed that the nitrogen atom in this alkaloid and in cevadine, like the nitrogen atom of hydroberberine, belongs to a double ring system.

Experimental:—The monobenzoyl cevadine was made by heating cevadine with benzoic anhydride to about 106° for 3 hours. The benzoate of benzoyl cevadine formed in the reaction is very difficultly soluble in water, a little more soluble in ether and very easily soluble in alcohol, acetone or benzol. It contains one molecule of water of crystallization which is not removed even at 120°.

From this benzoate the free benzoyl cevadine was liberated by ammonia and purified by dissolving it in warm alcohol containing a little glacial acetic acid and reprecipitating it with ammonia.

On warming the benzoyl cevadine with acetic anhydride it went into solution without becoming acetylized.

For the estimation of the benzoyl groups the benzoyl cevadine was saponified by means of alcoholic potassium hydroxide, the alcohol distilled off and, after adding sulphuric acid, the benzoic and tiglic acids driven over with steam and titrated with standard alkali. When pure cevadine is saponified a molecule of tiglic acid is split off quantitatively.

The benzoyl cevadine forms a hydrochloride which can be obtained by warming benzoyl cevadine with hydrochloric acid and water. The hydrochloride contains one molecule of water of crystallization.

A hydriodide of benzoyl cevadine can be prepared either by treat-

ing the solution of the hydrochloride with potassium iodide or by rubbing up benzoyl cevadine with hydriodic acid.

A nitrate of benzoyl cevadine can be obtained by rubbing up benzoyl cevadine with nitric acid.

Acetyl cevadine was made by boiling for a few minutes cevadine with acetic anhydride and, after adding excess of ammonia, shaking out the liquid with ether. The acetyl cevadine when heated melts at first at 182°, then becomes solid on further heating and melts again at 234°. The acetyl cevadine was converted into a hydrochloride by adding hydrochloric acid to its alcoholic solution and evaporating the liquid to dryness in vacuum.

Dibenzoyl cevine was prepared by the same method described above for the preparation of benzoyl cevadine.

The estimation of the benzoyl groups was made by saponifying the dibenzoyl cevine with alcoholic potassium hydroxide and, after making the liquid acid, extracting and weighing the benzoic acid.

A hydrochloride of dibenzoyl cevine was obtained by rubbing up the benzoate of dibenzoyl cevine with hydrochloric acid and removing the benzoic acid with ether. A difficultly soluble nitrate and an acetate of dibenzoyl cevine were also prepared.

Diacetyl cevine was obtained in the same way as the monoacetyl cevadine.

Cevine oxide was prepared by gently warming cevine with double its amount of hydrogen peroxide (30%) for about twenty minutes and recrystallizing the product from diluted alcohol. The estimation of nitrogen in the cevine oxide had to be carried out by Kjeldahl's method as Dumas' method gave too high results. A hydrochloride and a chloraurate of cevine oxide where also prepared.

On adding ammonia to a solution of hydrochloride of cevine oxide the liquid remains clear in the cold but on warming the solution the free cevine oxide crystallizes out.

When a current of sulphur dioxide is passed into a chloroformic solution of cevine oxide a double compound is formed according to following equation:

$$C_{27}H_{43}O_8{:}N{:}O + SO_2 = C_{27}H_{43}O_8{:}N\begin{cases} O \\ | \\ SO_2 \end{cases}$$

When this double compound is dissolved in water it is decomposed into cevine and sulphuric acid which can be removed by barium chloride. The reaction takes place according to following equation:

$$C_{27}H_{43}O_8{:}N\begin{cases}\diagup O\\ \quad |\\ \diagdown SO_2\end{cases} + H_2O = C_{27}H_{43}O_8{:}N + H_2SO_4$$

The cevine set free in this reaction was identified after extracting it from the liquid by chloroform in presence of sodium carbonate, by its potassium salt and by converting it again into cevine oxide.

Ber. Dtsch. chem. Ges., 1904, p. 1946.

**Cinchona Alkaloids.** A. Christensen continues his investigations of the bromine derivatives of the cinchona alkaloids.

Cinchonidine dibromide, $C_{19}H_{22}ON_2Br_2$, was prepared by the same method as cinchonine dibromide. (See Progress in Alkaloidal Chemistry during 1903, this Review 1904.)

The author finds that the compound made by Skalweit (Ann. Chem. Phar., 172, p. 102) and named by him dibromcinchonidine supposing it to be a substitution product of cinchonidine is identical with cinchonidine dibromide and that the dioxycinchonidine of Skalweit does not exist.

The author has also repeated the experiments of Galimard (Bull. Soc. Chim. [3] 25, p. 84) on $\alpha$ and $\beta$ dibromcinchonidine and found that these compounds too were not substitution products but addition products.

Monobromcinchonidine, $C_{19}H_{21}BrON_2$, was made by boiling the cinchonidine dibromide with twenty parts of alcohol and then adding half a part potassium hydroxide dissolved in alcohol. The monobromcinchonidine crystallizes in microscopic needles free from water of crystallization, turns the plane of polarization to the left and is insoluble in water but soluble in ether or alcohol. It forms an oxalate and a hydrobromide, $C_{19}H_{21}BrON_2.2HBr + 2H_2O$. Attempts to make a hydrobromide containing only one molecule of hydrobromic acid were not successful.

Dehydrocinchonidine was prepared by boiling cinchonidine dibromide with ten parts of alcohol and one part potassium hydroxide for twenty hours and then passing into the liquid a current of carbon dioxide. The dehydrocinchonidine forms a crystalline powder melting at 194° and corresponds to the formula $C_{19}H_{20}ON_2$. It is easily soluble in chloroform but difficultly soluble in alcohol.

Dibromcinchonidine hydrobromide perbromide $C_{19}H_{20}Br_2ON_2.2HBr.Br_2$, was prepared by heating a solution of dihydrocinchonidine in glacial acetic acid containing hydrobromic acid and bromine.

The perbromide is insoluble in ether, difficultly soluble in glacial acetic acid and, unlike the perbromide of cinchonidine dibromide, does not loose bromine on exposure to the air.

Dibromcinchonidine, $C_{19}H_{20}Br_2ON_2$, was prepared from the above perbromide by reducing the latter with sulphurous acid and precipitating the brominated base with ammonia. The dibromcinchonidine is extremely easily soluble in alcohol but can be recrystallized from a mixture of alcohol and chloroform.

Quinine dibromide, $C_{20}H_{24}O_2N_2Br_2$, is best prepared by a method similar to that of preparing cinchonine dibromide (Journ. pr. Chem., 63, p. 334; 68, p. 428). Ordinary (not anhydrous) quinine is dissolved in glacial acetic acid containing the theoretical amount of hydrobromic acid and to the solution is added the theoretical amount of bromine. After diluting the liquid with a little water a considerable excess of ammonium nitrate is added to the solution. The nitrate of quinine dibromide soon separates out and the free base can be liberated from the nitrate by means of ammonia.

By treating the quinine dibromide with silver nitrate or by prolonged boiling of the dibromide with lead acetate it is possible to remove one molecule of hydrobromic acid from the compound, but the resulting monobromquinine seems to undergo some change by this treatment as the free alkaloid thus obtained does not form any crystalline salts with acids.

Monobromquinine, $C_{20}H_{23}BrO_2N_2$, can be obtained by treating an alcoholic solution of quinine dibromide with an excess of alcoholic potassium hydroxide in the cold. The monobromquinine melts at 210°, is difficultly soluble in alcohol, has the specific rotation —118.1°, gives the thalleioquin reaction and forms fluorescent solutions. A hydrochloride of monobromquinine crystallizing with various amounts of water of crystallization, a hydrobromide crystallizing both with and without water of crystallization, a sulphate and an iodosulphate were also obtained.

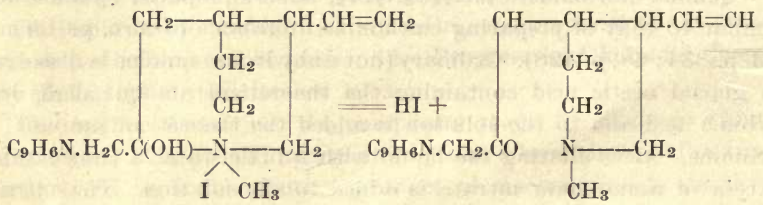
Dehydroquinine, $C_{20}H_{22}O_2N_2$, was prepared by heating quinine dibromide with five parts alcohol and half a part of potassium hydroxide for twenty hours and then passing into the liquid a current of carbon dioxide.

The dehydroquinine was purified by converting it into the oxalate and setting the base free by ammonia. It gives the thalleioquin

reaction and forms fluorescent solutions. A hydrochloride and a herapathite of the dehydrobase were also obtained.

When treated with bromine dehydroquinine seems to be converted into dibromquinine, $C_{20}H_{22}Br_2O_2N_2$. Journ. pr. Chem., 69, p. 193.

**Cinchonine.** P. Rabe and W. Denham find that when the iodomethylate of cinchonine is heated in acetic acid solution hydriodic acid is eliminated and methyl cinchotoxin is formed.

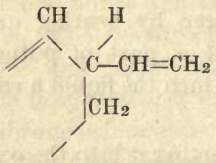


Cinchonine iodomethylate. Methylcinchotoxin.

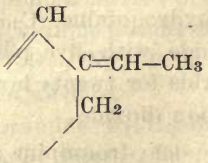
This transformation in acid solution is similar to the one which takes place in alkaline solution as observed by previous investigators (Claus and Miller, Ber. Dtsch. chem. Ges., 13, p. 2293; Freund and Rosenstein, Annal. Chem. Phar., 277, p. 279).

Ber. Dtsch. chem. Ges., 1904, p. 1674.

Zd. H. Skraup and R. Zwerger have tried to establish the structural formulas of the four isomeric bases: cinchonine, $\alpha$-i-cinchonine, $\beta$-i-cinchonine and allocinchonine. In a previous paper it had been shown that it is possible to ascribe to these isomeric bases such formulas as would account for the formation of one and the same hydriodocinchonine through the addition of hydriodic acid to any of them ond also for the formation of all these isomeric bases from this hydriodocinchonine when hydriodic acid is splitt off from it.



1



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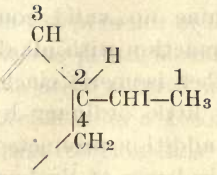
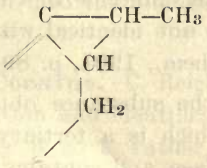
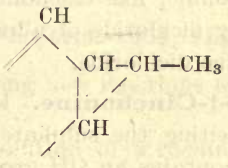


Hydriodocinchonine.



3



4

It can be seen that if the four isomeric cinchonine bases be supposed to correspond respectively to 1, 2, 3 and 4, the formation of all of them from the same hydriodocinchonine can be explained by assuming that the hydrogen which goes out together with the iodine comes from a different one of the numbered carbon atoms of the hydriodocinchonine for each of the iso bases.

On trying to verify these considerations by making a hydrochlor addition product of *α*-i-cinchonine and then splitting off again the hydrochloric acid, it was found that in the action of hydrochloric acid upon *α*-i-cinchonine the chief product is ordinary hydrochlor cinchonine and that only a small amount of hydrochlor-*α*-i-cinchonine is formed as a secondary product. It was also found that ordinary hydrochlorcinchonine is partly converted into hydrochlor-*α*-i-cinchonine when the former is heated under pressure with concentrated hydrochloric acid. It is therefore reasonable to assume that the little hydrochlor-*α*-i-cinchonine formed in the first reaction is only a product of transformation of ordinary hydrochlorcinchonine.

It was further found that on splitting off hydrochloric acid by means of alkali one and the same base, namely, cinchonine was obtained from hydrochlorcinchonine as well as from hydrochlor-*α*-i-cinchonine. This fact can of course not be explained by ascribing to the four iso-bases the formulas given above according to which we ought to get different bases from different hydrochlor derivatives. But as hydrochlorcinchonine is under certain conditions transformed

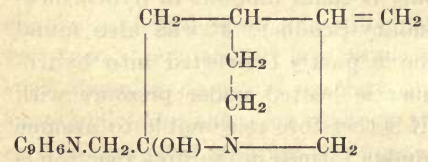
into hydrochlor-α-i-cinchonine no valid conclusions can be drawn from the products of the reaction with alkali.

On subjecting the other isomeric cinchonines to the action of hydrochloric acid only a little ordinary hydrochlorcinchonine was obtained but no isomeric addition products could be isolated.

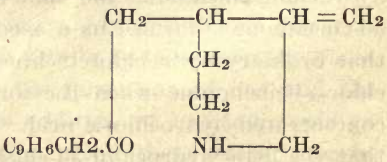
On treating the three isobases of cinchonine with chlorine it was found that α- and β-i-cinchonine did not react at all, but, that allocinchonine, like cinchonine itself, took up one molecule of chlorine giving dichloride of allocinchonine which was not identical with cinchonine dichloride. Monatshefte f. Chem., 1904, p. 894.

**β-i-Cinchonine.** K. Kaas finds that the substance obtained by melting the sulphate of β-i-cinchonine (which is a tertiary base and contains an OH group) is a secondary base and contains a CO group. As the transformation is the same as that which takes place when tertiary cinchonine containing an OH group is changed to secondary cinchonicine containing a CO group, the substance obtained by melting β-i-cinchonine sulphate should be named β-i-cinchonicine, not β-i-pseudocinchonicine as had been proposed.

That β-i-cinchoninicine is really a secondary base was shown by the formation of the hydriodide of N-methyl β-i-cinchonicine when the base is treated with methyl iodide. The presence of a $CH_3$ group linked to the nitrogen atom in the methylated base was shown by Herzig and Meyer's method and that the $CH_3$ group was not linked to oxygen was shown by the negative results obtained by Zeisel's method.




Cinchonine.




Cinchonicine.

Another anology between β-i-cinchonicine and cinchonicine was found in the fact that when the iodomethylate of β-i-cinchonine is heated with potassium hydroxide, hydriodic acid is eliminated and the resulting compound is identical with the one obtained by methylating β-i-cinchonicine. In exactly the same way the iodomethylate of cinchonine when heated with potassium hydroxide is converted into methylcinchonicine. (See page 123.)

An attempt to prove the presence of a CO group in β-i-cinchonicine by means of phosphorus pentachloride did not give the desired results: only one chlorine atom entered into the compound instead of two as should be expected from a ketone. As there was evolution of hydrochloric acid in this reaction it is probable that at first the oxygen atom of the CO group is replaced by two chlorine atoms but that the dichlorcompound soon looses hydrochloric acid and is converted into the monochlorderivative.

Monatshefte f. Chem. 1904, 1145.

**Cocaine.** C. Reichard gives the following new reactions for the detection and identification of cocaine.

1. If to a rather concentrated cold solution of a cocaine salt a solution of sodium nitroprusside be added the solution becomes turbid and, with the aid of a magnifying glass, small crystals of a reddish color can be noticed in the liquid. Morphine salts do not give this reaction.

2. If to a quite concentrated solution of cocaine hydrochloride a strong solution of uranium nitrate be added a yellow crystalline precipitate is formed which is most probably a double salt of cocaine and uranium.

3. If some titanic acid be dissolved in warm concentrated sulphuric acid and to the cooled solution be added some cocaine hydrochloride there is no reaction whatever in the cold even on prolonged standing. But if the mixture be warmed in a porcelain dish till stripes and oily drops appear on the sides of the vessel a beautiful blue or violet color is developed which is very stable. On adding water to the liquid a blue precipitate settles at the bottom of the vessel. The reaction is undoubtedly due to the reduction of titanic acid by the methyl alcohol formed in the saponification of the alkaloid by the sulphuric acid.

4. If to a mixture of potassium methylsulphate and sulphuric acid a little cocaine hydrochloride be added and the mixture warmed a strong peppermint odor is developed which is permanent for a long time.

5. On warming cocaine hydrochloride with a mixture of urea and sulphuric acid the mixture assumes a blue color which becomes deeper as the temperature rises. If in this reaction ethylene diamine be substituted for urea there is first an evolution of hydrochloric acid but on applying heat the blue color appears.

Chem. Ztg., 1904, p. 299.

C. E. Carlson finds that in testing cocaine hydrochloride for the presence of reducing substances (cinnamyl cocaine) by means of potassium permanganate and sulphuric acid it is best to leave out the sulphuric acid altogether. The sulphuric acid seems to retard the velocity of the reaction changing in some way the reducing substance. It was also found that if the sulphuric acid be added after the potassium permanganate the retardation is less than when the order is reversed. Pharm. Centralhalle, 1904, p. 69.

**Coffearine.** L. Graf corroborates the statement of P. Paladino (Ber. Dtsch. Chem. Ges. 1894, 406. R.) about the existence in coffee of the alkaloid coffearine.

That this alkaloid is not formed by the action of the calcium oxide, which Paladino used in his method of extraction, upon coffeine was shown by the fact that no coffearine could be obtained by the author from coffeine by treating it with calcium oxide. On the other hand coffearine was obtained from aqueous extracts of coffee even without the use of calcium oxide.

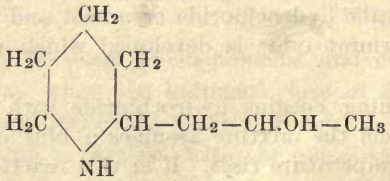
The formula of coffearine, $C_{14}H_{16}N_2O_4$, established by Paladino was found to be correct.

Zeitschr. öffentl. Chem., 1904, p. 280.

**Conhydrine.** K. Löffler has investigated the constitution of conhydrine, pseudoconhydrine and of some of the coniceines.

As both conhydrine and pseudoconhydrine give the same α-pipecolinic acid upon oxidation the OH group in both these bases must be situated in the side chain (Willstätter, Ber. Dtsch. Chem. Ges. 34, 3166).

Of the three theoretically possible oxypiperidines containing the OH group in the side chain one was prepared synthetically by Ladenburg and found to have the constitution of an α-pipecolylmethylalkine




α-Pipecolylmethylalkine.

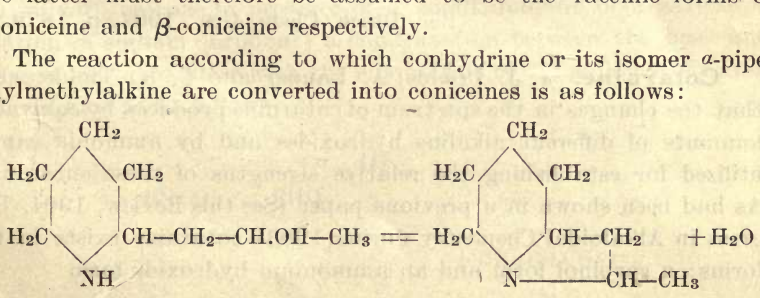
As there are two assymetric carbon atoms in this compound it

ought to exist in four optically active modifications and two racemic modifications. Conhydrine and pseudoconhydrine can be assumed to be two of the four optically active forms; the synthetic α-pipecolylmethylalkine is one of the racemic modifications and is chemically identical with conhydrine.

The chemical identity of conhydrine with α-pipecolylmethylalkine was shown by the following experiments:

1. On heating the synthetic α-pipecolylmethylalkine with fuming hydrochloric acid to 220° water is eliminated and two isomeric bases are formed which are very similar to α-coniceine and β-coniceine respectively previously obtained from conhydrine by the same method. The salts obtained from the two bases were also found to be almost identical with those obtained from α-coniceine and β-coniceine respectively. The only difference between α-coniceine and -coniceine on one hand and the bases obtained from α-pipecolylmethylalkine on the other is that the former are optically active while the latter are inactive. The latter must therefore be assumed to be the racemic forms of α-coniceine and β-coniceine respectively.

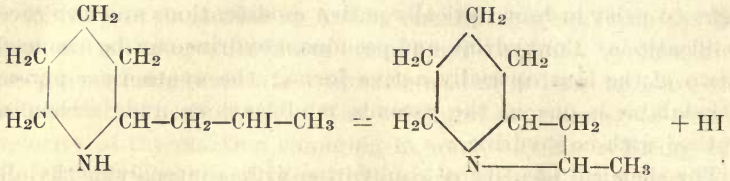
The reaction according to which conhydrine or its isomer α-pipecolylmethylalkine are converted into coniceines is as follows:




Conhydrine. Coniceine.

2. On heating α-pipecolylmethylalkine with hydriodic acid and amorphous phosphorus two isomeric compounds are obtained which contain an atom of iodine instead of the OH group. Both these iodine containing bases behave exactly like the iodine derivatives obtained from conhydrine by the same method.

3. On treating the iodine compounds obtained from the α-pipecolylmethylalkine with sodium hydrate, hydriodic acid is eliminated and the bases thus obtained are identical with ε-coniceine previously obtained by Lellmann from conhydrine by the same method, i. e., replacing the OH group by iodine and then splitting off hydriodic acid by means of alkali. The reaction takes place according to the following equation:



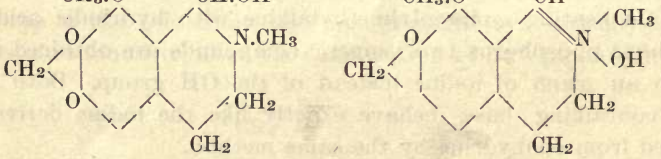
Jodoconiine. ε-Coniceine.

The only difference between ε-coniceine and the bases obtained from the iodine derivative of α-pipecolylmethylalkine is that ε-coniceine is optically active while the bases from α-pipecolylmethylalkine are inactive. We can again assume that these bases are the two racemic forms of ε-coniceine.

Attempts to split up synthetic α-pipecolylmethylalkine into its active components and thus obtain bases in every respect identical with conhydrine and pseudoconhydrine were not successful. No crystalline compounds could be isolated.

Ber. Dtsch. Chem. Ges., 1904, p. 1879.

**Cotarnine.** J. J. Dobbie, A. Lauder and C. K. Tinkler show that the changes in the spectrum of cotarnine produced by equivalent amounts of different alkaline hydroxides and by ammonia can be utilized for establishing the relative strengths of these substances. As had been shown in a previous paper (See this Review, 1904, Progress in Alkaloidal Chemistry during 1903) cotarnine exists in two forms: a carbinol form and an ammonium hydroxide form



Carbinol form. Ammoniumhydroxide form.

which have different spectra both in the free condition and as salts. The addition of alkali to a solution of the yellow ammonium form changes the cotarnine to the colorless carbinol form. On using equivalent amounts of different alkaline hydroxides and ammonia and observing the changes produced in the spectra it was found that

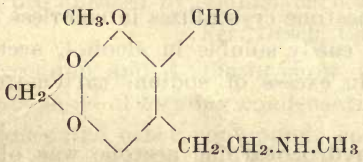
the relative strengths of the different alkalies are the same as found by other methods.

The action of sodiumhydroxide on an aqueous solution of cotarnine (containing the ammonium form) can be explained by assuming that the solution contains a mixture in equilibrium of the undissociated ammonium form together with the OH and the other ion resulting from its dissociation, with practically none of the carbinol form. By the addition of sodium hydroxide the active mass of the OH ions is increased and the dissociation of the ammonium form is diminished. The ammonium form then passes into the carbinol form, in which the dissociation is at a minimum, until the equilibrium is restored. The further addition of sodium hydroxide leads to a repetition of these changes until the ammonium form is practically all converted into the carbinol form.

Journ. Chem. Soc., 1904, p. 121.

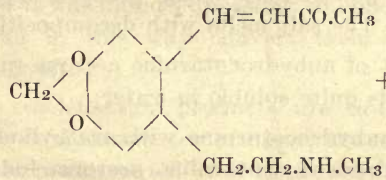
According to C. Liebermann and F. Kropf when cotarnine is shaken with acetone in presence of a small amount of a saturated solution of sodium carbonate a condensation between the base and the acetone takes place with the elimination of one molecule of water. The reaction is as follows:

**(I)**




$+ CH_3.CO.CH_3 =$

Cotarnine.

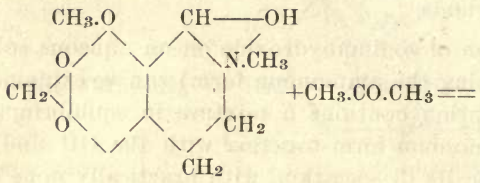



$+ H_2O$

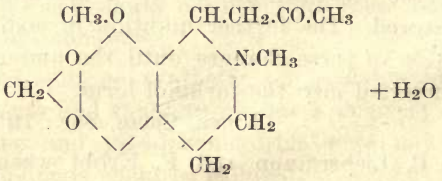
Anhydrocotarnine acetone.

If the cotarnine be supposed to react in its tautomeric form the equation can be written in the following way:

(II)




Cotarnine (tautomeric form.)




Anhydrocotarnine acetone.

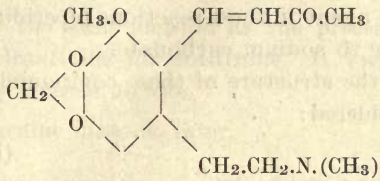
A similar condensation of cotarnine takes place with other ketones containing a $CH_3$ group and also with such substances which, like malonic ester, contain a $CH_2$ group between carbonyl groups.

The anhydrocotarnine acetone crystallizes in colorless or slightly yellowish prisms which are easily soluble in alcohol, acetone, ether and benzol but insoluble in excess of sodium carbonate. Melting point 83°.

A hydrochloride of anhydrocotarnine acetone was obtained by passing hydrochloric acid gas into an ethereal solution of anhydrocotarnine acetone and recrystallizing the salt from a mixture of alcohol and ether. The salt melts with decomposition at 171°.

A platinum salt of anhydrocotarnine acetone was also obtained. The platinum salt is quite soluble in water.

On digesting anhydrocotarnine with methyliodide at ordinary temperature anhydromethylcotarnine acetone iodomethylate was obtained. It crystallizes from hot water in small colorless plates melting at 144°. The hydriodide of an hydrocotarnine acetone formed in the reaction being more soluble than the quaternary base was removed by cold water.




Anhydromethyl cotarnine acetone iodomethylate.

On converting the iodomethylate by means of silver chloride into the corresponding chloromethylate and treating the latter with platinum tetrachloride the corresponding chloroplatinate was obtained.

Anhydrocotarnine methylpropyl ketone, $C_{17}H_{23}NO_4$, was prepared by the same method as the acetone compound. It had no sharp melting point.

Anhydrocotarnine acetophenone was prepared in the same way as the acetone compound. The acetophenone condensation product is easily soluble in benzol and in warm alcohol. It crystallizes in colorless prisms melting at 126° and forms a yellowish platinum salt.

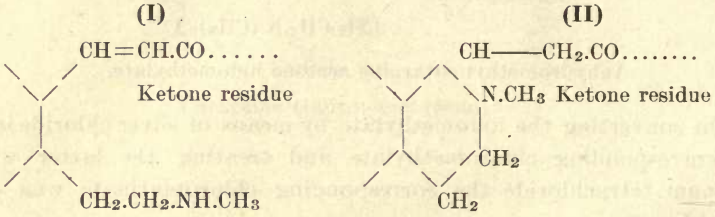
Anhydrocotarnine malonic ester was prepared by the same method as the other condensation compounds. It forms crystals and is not precipitated by sodium carbonate from its solutions in acids. Ber. Dtsch. Chem. Ges., 1904, p. 211.

C. Liebermann and A. Clawe show that cotarnine and hydrastinine are capable of forming condensation products not only with methyl ketones and other compounds containing methylene carbon atoms between carbonyl groups (see preceeding paragraph), but with a great many other compounds, like coumarone, resorcin, etc. On the other hand it was found impossible to condense the two bases with meconin and in this way convert them into narcotine and hydrastine respectively.

The various condensation products are not all equally stable. The malonic ester compounds, for example, are so easily decomposed that the free bases are liberated even in the simplest reactions, while some of the other condensation products are not decomposed unless boiled or digested for some time with strong mineral acids. In these decompositions the compounds always break up into their component parts.

As a condensing agent in these reactions piperidine was frequently found to be superior to sodium carbonate.

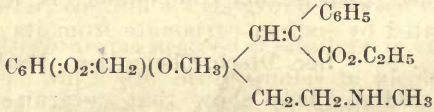
With regard to the structure of these compounds there are two formulas to be considered:




As (I) is a secondary and (II) a tertiary base experiments were made with a view to establish the constitution by making alkyl and acyl derivatives of the compounds. (See next paragraph.) It was found that for some of the condensation products (I) must be accepted while for others (II) is preferable. The formulae are, therefore, tautomeric.

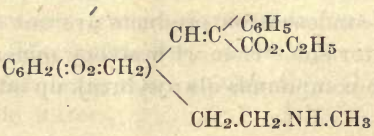
The condensation products prepared in this investigation are as follows:

Anhydrocotarnine phenylacetic ester,



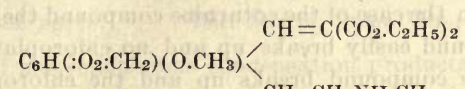

This compound was prepared by digesting cotarnine with phenyl acetic ester in alcoholic solution in presence of sodium carbonate, removing the unattacked ester by means of ether and purifying the condensation product by precipitating it from its acid solution with sodium carbonate and recrystallizing from alcohol. The anhydrocotarnine phenyl acetic ester forms a platinum salt and a difficultly soluble nitrate. On warming it with hydrochloric acid the liquid becomes turbid and phenylacetic ester separates out.

Anhydrohydrastinine phenylacetic ester,



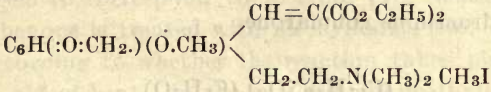
was prepared by the same method as the preceeding compound but substituting hydrastinine for cotarnine. It forms a platinum salt but no difficultly soluble nitrate.

Anhydrocotarnine malonic ester,



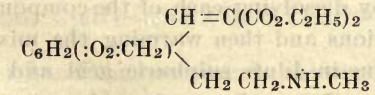
was made by gently warming a mixture of cotarnine and malonic ester with a few drops of piperidine and then setting the mixture aside for twenty-four hours. The malonic ester compound is very easily decomposed by hot solvents or by digestion with hydrochloric acid. On trying to make a platinum salt of it by adding chloroplatinic acid and the calculated amount of hydrochloric acid, the platinum salt of cotarnine itself was obtained instead, and from the mother liquor of the platinum salt it was possible to isolate and identify both malonic acid and malonic ester, showing that the condensation product is easily transformed into cotarnine malonate.

Anhydromethyl cotarnine malonic ester iodomethylate,



was formed together with cotarnine hydriodide on digesting the preceeding malonic ester condensation product with methyl iodide at ordinary temperature and removiug the hydriodide by washing with cold water in which the salt is much more soluble than the quaternary compound. The iodomethylate was then recrystallized from hot water.

Anhydrohydrastinine malonic ester,



was obtained by the same method as was used for the preparation of the corresponding cotarnine compound. As the hydrastinine com-

pound is very easily soluble in alcohol it was isolated by concentrating the alcoholic solution in vacuum over calcium chloride, then taking up the residue with ether and evaporating the ether in vacuum. The hydrastinine compound becomes yellowish on exposure to light and is as easily decomposed as the corresponding cotarnine compound. As in the case of the cotarnine compound the anhydrohydrastinine compound easily breaks up and no chloroplatinate could be obtained: the compound breaks up and the chloroplatinate of hydrastinine is formed instead of the chloroplatinate of the condensation product.

Anhydrocotarnine coumarone,

$$(C_{12}H_{14}NO_3).(C_8H_5O)$$

was made by digesting cotarnine with coumarone in alcoholic solution in presence of sodium carbonate and, after 24 hours' standing, precipitating the condensation product with water. It was purified by dissolving it in hydrochloric acid, precipitating the solution with sodium carbonate, then redissolving the precipitate in ether and precipitating it again with ligroin. The compound forms a yellow flocculent platinum salt.

Anhydrohydrastinine coumarone.

$$(C_{11}H_{12}NO_2).(C_8H_5O)$$

was prepared in the same way as the preceeding compound. It forms a platinum salt and dissolves in concentrated sulphuric acid with violet color.

Anhydrocotarnine resorcin,

$$(C_{12}H_{14}NO_3).[C_6H_3(OH)_2]$$

can be made either by dissolving each of the components in alcohol, mixing the two solutions and then warming the mixture to 60° or by dissolving cotarnine in dilute sulphuric acid and adding to this solution an alcoholic solution of resorcin. After standing a few days the liquid is diluted with water and the condensation product precipitated with sodium carbonate. The compound is easily soluble in

dilute acids and is reprecipitated from acid solutions by potassium hydrate or potassium carbonate. An excess of potassium hydrate redissolves the precipitate. It forms a hydrochloride which is difficultly soluble in hydrochloric acid. Boiling hydrochloric acid decomposes the condensation product only slowly and incompletely into its component parts. Ber. Dtsch. Chem. Ges., 1904, p. 2738.

L. Kropf has made some condensation products of cotarnine and tried to establish the formulae of these compounds by proving the presence or absence of a hydrogen atom attached to the nitrogen atom in these compounds. (See the two preceeding paragraphs.) In anhydrocotarnine acetophenone and anhydrocotarnine acetone the presence of such an atom was shown by the fact that these compounds can be converted into acetyl and benzoyl derivatives. It was found that the benzoyl derivative made from anhydrocotarnine acetone was identical with the compound made by condensing acetone with benzoyl cotarnine in which the benzoyl group has the same position as the hydrogen atom in cotarnine, i. e., it must be attached to the nitrogen atom. These condensation products must correspond, therefore, to formula (I). (See preceeding paragraph).

In the reaction of some of these compounds with methyliodide they also seem to correspond to formula (I). When anhydrocotarnine acetophenone is treated with methyliodide two compounds are obtained according to whether the reaction takes place in the cold or with the aid of heat. In the cold the iodomethylate of anhydromethylcotarnine acetophenone is formed together with the hydriodide of anhydromethylcotarnine acetophenone. In the heat the hydriodide of anhydromethylcotarnine acetophenone is formed. These compounds too must correspond to formula (I) and their formation can be expressed by following equations:

1. In the cold. $2C_{19}H_{17}O_4NH.CH_3 + 2CH_3I = C_{19}H_{17}O_4N(CH_3)_3I + C_{19}H_{17}O_4NH.CH_3.HI$.

2. In the heat. $C_{19}H_{17}O_4NH.CH_3 + CH_3I = C_{19}H_{17}O_4N(CH_3)_2.HI$.

On the other hand the compounds obtained by condensing cotarnine with ethylacetoacetic ester or benzylacetoacetic ester both of which contain only one hydrogen atom attached to the carbon atom which takes part in the condensation, must correspond to formula

(II), that is, the alkaloid must be supposed to react in the tautomeric form containing a OH group which is eliminated with the hydrogen atom of the esters as water.

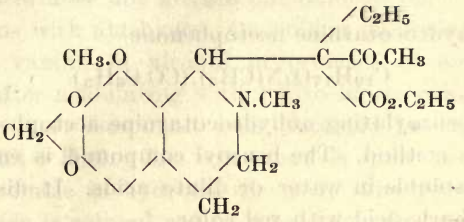
Experimental. Anhydrocotarnine acetylacetone $C_{17}H_{21}NO_5$ was prepared by warming molecular quantities of cotarnine and acetylacetone in presence of alcohol and some saturated solution of sodium carbonate. On slowly cooling the liquid and adding water to it the condensation product is precipitated as a yellowish white crystalline powder. It was purified by solution in dilute hydrochloric acid and recrystallization from diluted alcohol. It forms a hydrochloride which can be obtained by passing hydrochloric acid gas into its ethereal solution and recrystallizing the salt from ether-alcohol. The hydrochloride is very hygroscopic. A platinum salt was prepared which crystallizes in yellow needles and is quite soluble in warm water.

Anhydrocotarnine acetonylacetone, $C_{18}H_{23}NO_5$, was made by warming an alcoholic solution of the components in presence of some sodium carbonate, then adding to the cooled mixture enough hydrochloric acid to make a clear solution and precipitating the condensation product with sodium carbonate. The oily liquid which separates out is taken up with ether, the ether evaporated and the residue, after solution in hydrochloric acid, again precipitated with sodium carbonate. The precipitate is again dissolved in ether and the ether removed by evaporation. The condensation product forms a white crystalline powder which is very easily soluble in alcohol or ether but insoluble in water. It forms a hygroscopic hydrochloride and a yellow flocculent platinum salt.

Anhydrocotarnine acetoacetic ester, $C_{18}H_{23}NO_6$, was made in the same way as the acetylacetone compound. It forms a hygroscopic hydrochloride and a platinum salt.

Anhydrocotarnine benzoylacetoacetic ester, $C_{23}H_{24}NO_6$, was obtained in the same way as the preceeding compound. By the same method was prepared anhydrocotarnine cyanoacetoacetic ester, $C_{17}H_{20}N_2O_5$. The cyanogen compound cannot be dissolved in hydrochloric acid without decomposition and on trying to make a platinum salt of it the platinum salt of cotarnine was formed.

Anhydrocotarnine ethylaceto acetic ester,



was prepared by the same method as the acetoacetic ester compound. It could not be obtained in solid condition and was, therefore, converted into the hydrochloride for analysis.

The corresponding benzylacetoacetic ester compound was obtained by the same method in the form of an oil. It gives a hydrochloride and a platinum salt.

Iodomethylate of anhydromethylcotarnine acetophenone, $C_{22}H_{26}O_4NI$, was obtained by digesting the components under cooling and removing the hydriodide of anhydrocotarnine acetophenone formed at the same time by washing with a little water or alcohol in which the hydriodide is more soluble than the iodomethylate. The iodomethylate forms yellowish white needles quite soluble in warm alcohol or warm water. It is not precipitated from its aqueous solution by alkalies or alkaline carbonates.

If methyliodide and cotarnine acetophenone are made to react upon each other without cooling the mixture becomes hot and on cooling the hydriodide of anhydromethylcotarnine acetophenone separates out in crystals. From the hydriodide the free anhydromethylcotarnine acetophenone is precipitated by alkalies or alkaline carbonates as an oily liquid which very soon becomes crystalline. The base dissolves in concentrated sulphuric acid with a red color.

Acetylanhydrocotarnine acetophenone,

$$C_{19}H_{17}O_4[N.(CH_3).(CO.CH_3)]$$

was prepared by digesting on the water bath anhydro-cotarnine acetophenone with acetic anhydride. The liquid was then boiled with water and after cooling the acetyl derivative precipitated with sodium carbonate. The acetyl compound is oily at first but soon becomes

crystalline. It dissolves in concentrated sulphuric acid with a blood-red color.

Benzoylanhydrocotarnine acetophenone

$$C_{19}H_{17}O_4N(CH_3).(CO.C_6H_5)$$

was made by benzoylating anhydrocotarnine acetophenone by Schotten-Baumann's method. The benzoyl compound is easily soluble in alcohol but insoluble in water or dilute acids. It dissolves in concentrated sulphuric acid with red color.

Benzoylanhydrocotarnine acetone,

$$C_{11}H_{15}O_4N(CH_3).(CO.C_6H_5)$$

was made by benzoylating anhydrocotarnine acetone by Schotten-Baumann's method. It is oily at first but becomes crystalline in vacuum. It is easily soluble in alcohol but insoluble in water or dilute acids.

The compound can be made by condensing benzoylcotarnine (Ann. d. Chem. 254, 335) with acetone. For this purpose the benzoylcotarnine is warmed with acetone on the water bath in presence of some alcoholic potassium hydrate. After twelve hours the benzoylated condensation product separates out in crystals.

Ber. Dtsch. Chem. Ges., 1904, p. 2744.

C. Renz and M. Hoffmann have tried to condense tetrahydromethoxyquinoline (the sulphate of which is used under the name of thalline) and cotarnine with aldehydes and phtalic anhydride. No condensation product could be obtained from thalline and aldehydes but with phtalic anhydride a definite compound was obtained according to following equation:

$$C_{10}H_{13}NO + C_6H_4(CO)_2O = C_{18}H_{15}NO_3 + H_2O$$

Whether the two hydrogen atoms which go out with one oxygen atom of the anhydride as water come from the methyl group situated in the benzol ring or from the reduced pyridine ring has not yet been established.

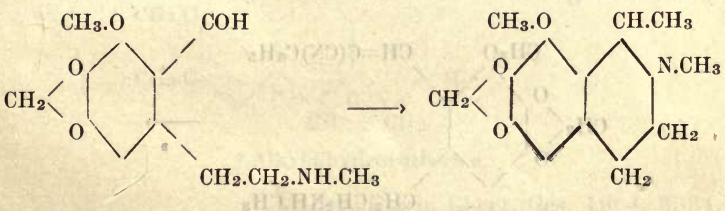
1. Thalline with phtalic anhydride. The condensation of thalline with phtalic anhydride was effected by heating molecular quantities of the substances to 370° and boiling the yellow vitreons reaction product with alcohol. The condensation product is insoluble in dilute acids or alkalies, soluble in boiling glacial acetic acid and strong sulphuric acid and slightly soluble in concentrated hydro-

chloric acid and benzol. It has the formula $2C_{18}H_{15}NO_3 + C_2H_6O$. Boiling nitric acid does not nitrate but oxidizes it.

2. Cotarnine with aldehydes. On boiling molecular quantities of cotarnine and vanilin in alcohol in presence of some potassium hydrate and, after acidulating with hydrochloric acid, evaporating off the alcohol a compound was obtained having the formula $C_{20}H_{17}NO_4 + HCl + H_2O$. The compound is quite soluble in water but difficultly soluble in hydrochloric acid. The yellow solution of the hydrochloride is colored red by ammonia. On standing the red color disappears. The free base could not be isolated.

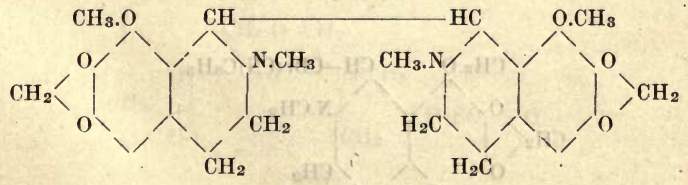
On substituting in the above reaction protocatechuic aldehyde for vanilin a compound was obtained having the formula $C_{19}H_{19}NO_6 . HCl + H_2O$. This compound too is colored red by ammonia. Neither the free base nor a gold or platinum salt of the compound could be obtained. Ber. Dtsch. Chem. Ges., 1904. p. 1962.

M. Freund finds that on subjecting cotarnine or its hydrochloride or cyanide to Grignard's reaction $\alpha$-substituted derivatives of hydrocotarnine can be obtained. For example, with $CH_3.Mg.I$ we get $\alpha$-methylhydrocotarnine



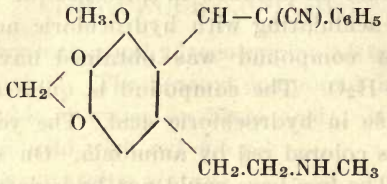

In the same way can be prepared compounds containing instead of the methyl group the ethyl, propyl, isobutyl, phenyl, $\beta$-naphtyl and benzyl groups.

If in Grignard's reaction allyliodide or polyhalogen derivatives of the hydrocarbons be used there is always formed di-hydrocotarnine




Di-hydrocotarnine.

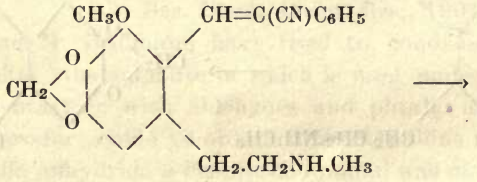
According to an observation of Roser when cotarnine is condensed with benzylcyanide anhydrocotarnine benzylcyanide is formed which is decomposed by acids into its components.

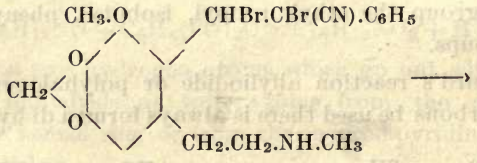


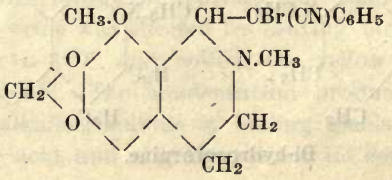

Anhydrocotarninebenzylcyanide.

This compound when treated with methyliodide is converted into the iodomethylate of anhydrocotarnine methine benzylcyanide, $(CH_3O).(CH_2O_2).C_6H[CH:C.(CN).C_6H_5].CH_2CH_2.N(CH_3)_3I$, which is decomposed by warm alkalies with the elimination of trimethylamine.

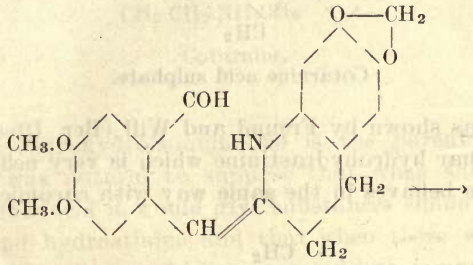
The author intends to convert the anhydrocotarnine benzylcyanide into the corresponding dibromide from which it ought to be possible to eliminate hydrobromic acid with the closing of the side chain into a ring:



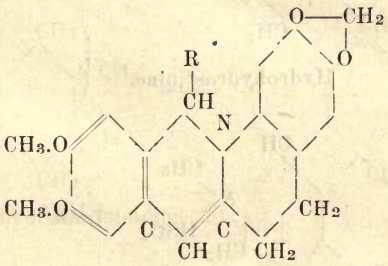



The author also finds, that berberinal which in some respects resembles cotarnine and hydrastinine is converted by means of alkyl magnesium iodide into α-alkyldihydroberberine:



Berberinal.

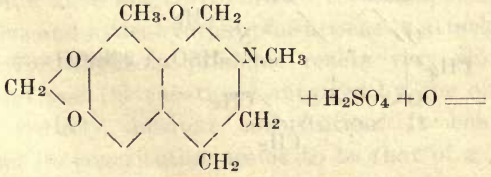


α-Alkyldihydroberberine.

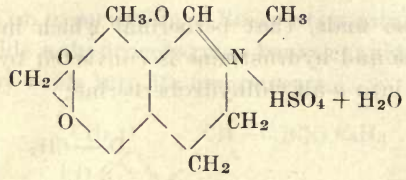
Ber. Dtsch. Chem. Ges. 1904, 3334.

M. Freund und H. Beck have investigated the action of chronic acid upon N-methyltetrahydroisoquinoline.

As Beckett and Wright had previously shown (Journ. Chem Soc. 1876, 577) hydrocotarnine is oxidized by chromic acid to a salt of cotarnine:

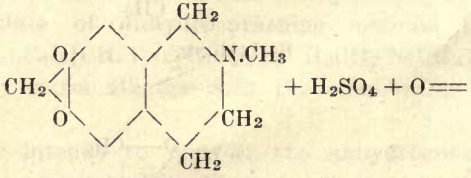


Hydrocotarnine.

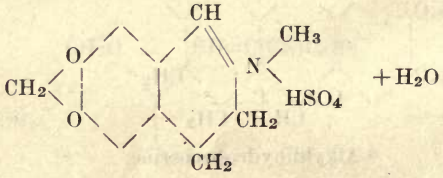



Cotarnine acid sulphate.

Later it was shown by Freund and Will (Ber. Dtsch. Chem. Ges. 1887, 2403) that hydrohydrastinine which is very nearly related to hydrocotarnine behaves in the same way with chromic acid.

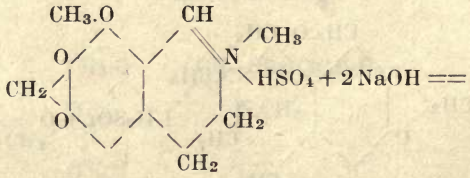



Hydrohydrastinine.

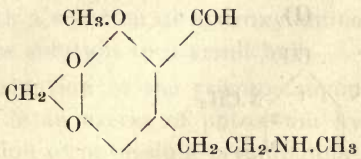



Hydrastinine acid sulphate.

On adding alkali to these salts of cotarnine and hydrastinine the bases are set free. In this reaction the reduced pyridine ring is opened up with the formation of an aldehyde group and a methylimide group:

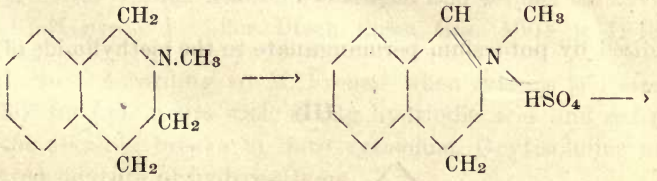



Cotarnine acid sulphate.

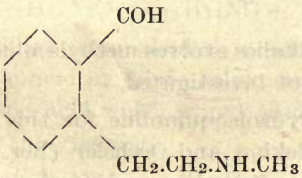



Cotarnine.

As N-methyltetrahydroisoquinoline is the parent substance of these bases it was natural to suppose that when subjected to the action of chromic acid it would give substances similar to the salts of cotarnine and hydrastinine and that when these substances are treated with alkali they would be converted into compounds containing a COH and an $NCH_3$ group.

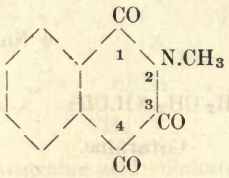



N-Methyltetrahydroisoquinoline.



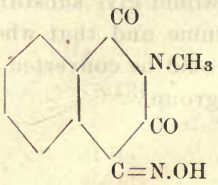

Experiments have not corroborated these suppositions. Whereas hydrocotarnine and hydrohydrastinine are easily attacked by chromic acid N-methyltetrahydroisoquinoline reacts very slowly with this oxidizing agent and the substance obtained by the oxidation seems to have an entirely different constitution. It has the formula $C_{10}H_7NO_3$ and its constitution seems to be that of a 1, 3, 4, -trike-to-N-methyltetrahydroisoquinoline.

(I)



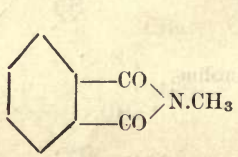

This compound reacts with hydroxylamine forming an oxime,

(II)




is oxidized by potassium permanganate to the methylimide of phtalic acid

(III)




and when boiled with alkalies evolves methylamine with the formation of an acid which was not investigated.

The N-methyltetrahydroisoquinoline for this work was obtained by the method of Wedekind and Oechsler (Ber. Dtsch. Ges., 1902, 3987) and its oxidation effected by means of potassium dichromate in presence of a large excess of sulphuric acid choosing the amount of the dichromate so as to have six atoms of oxygen for one molecule of the base. The triketocompound (I) was recrystallized from hot alcohol. It is not effected by dilute acids and is soluble in cold alkalies and hot solutions of sodium carbonate or ammonia. From these alkaline solutions the triketocompound cannot be recovered unchanged by addition of acid.

The monoxime (II) was obtained by digesting the triketocom-

pound with a solution of hydroxylamine hydrochloride and concentrating the solution to a small bulk.

The oxidation of the triketocompound was carried out by dissolving it in an excess of potassium hydrate, adding a three per cent solution of potassium permanganate and boiling the liquid for some time. On shaking out the mixture with ether and recrystallizing the substance from alcohol after evaporation of the ether, the compound was identified by comparing it with the methylimide of phtalic acid (III) which was prepared by neutralizing phtalic acid with methylamine, evaporating the liquid to dryness and melting the residue.

On boiling the triketocompound with a 50% solution of potassium hydrate till the evolution of methylamine ceased and shaking out, the liquid with ether after a cidulating with sulphuric acid a crystalline acid substance was obtained which gave crystalline barium and silver salts. It was free from nitrogen and seemed to have the formula $C_{15}H_{12}O_7$. Ber. Dtsch. Chem. Ges., 1904, p. 1942.

**Cytisine.** According to M. Freund when cytisine is heated to 225°—230° for four hours with strong hydriodic acid and red phosphorus the alkaloid breaks up into cytisoline, $\beta$-cytisolidine and a complicated mixture of hydrocarbons.

Cytisoline, $C_{11}H_{11}NO$. The formation of cytisoline from cytisine takes place according to following equation:

$$C_{11}H_{14}N_2O = C_{11}H_{11}NO + NH_3$$

Cytisoline crystallizes from alcohol in needles melting at 199°. Chromic acid in aeetic acid or dilute sulphuric acid solution oxidizes cytisoline to cytisolinic acid which would seem to indicate the presence of a $CH_3$ group in cytisoline:

$$C_{10}H_8(CH_3)NO \longrightarrow C_{10}H_8(CO_2H)NO.$$

The cytisolinic acid was purified by solution in hot glacial acetic acid and precipitation with water. The acid crystallizes in small needles melting above 350°. It is soluble in ammonia and is repricitated from the ammoniacal solution by mineral acids. It is a very stable substance not being affected by strong nitric acid or strong potassium hydroxide. A mixture of nitric and sulphuric acids converts cytisoline into nitrocytisoline which forms yellow crystals beginning to sinter at 240° and melting at 275°.

Sodium in absolute alcohol reduces cytisoline to α-cytisolidine, $C_{11}H_{15}N$, which is isomeric with β-cytisolidine obtained by the action of hydriodic acid and phosphorus upon cytisine. The α-cytisolidine is an oily liquid of a strong odor and forms a crystalline chloroplatinate and an oily picrate (difference from β-cytisolidine which forms a crystalline picrate).

β-Cytisolidine, $C_{11}H_{15}N$. As said above this compound is formed together with cytisoline by the action of strong hydriodic acid upon cytisine in presence of amorphous phosphorus. The two bases were separated from each other by ether which removes the weakly basic cytisoline leaving the strongly basic β-cytisolidine in the aqueous solution. The β-cytisolidine was then distilled with steam into dilute hydrochloric acid and converted first into a chloroplatinate and then (after removing the platinum by $H_2S$) into a picrate. The chloroplatinate melted at 207°. The picrate is at first semisolid but when rubbed with a glass rod becomes crystalline. It melts at 228°.

On decomposing the picrate of β-cytisolidine with sodium hydroxide, distilling off the β-cytisolidine and converting it again into a chloroplatinate the latter was found to have a melting point of 235°. Hence the above mentioned chloroplatinate of β-cytisolidine of the melting point 207° which was obtained directly without passing through the picrate must have been impure.

Ber. Dtsch. Chem. G. 1904, 16.

**Damascenine,** $C_9H_{11}NO_3$. H. Pommerehne shows that when damascenine is heated with hydriodic acid one methyl group is eliminated and the demethylized alkaloid is left in the form of a hydriodide crystallizing in colorless plates and melting at 198°—200°. The hydriodide was converted into the corresponding hydrochloride by means of silver chloride. The hydrochloride crystallizes in colorless spherical forms melting at 217°—218°.

Owing to the strong reducing properties of the demethylized damascenine no gold or platinum salt could be obtained from it. An attempt to acetylize it was likewise unsuccessful.

On heating damascenine hydrochloride with barium hydrate the alkaloid undergoes the same internal rearrangement as when boiled with alcoholic potassium hydrate, i. e.; the base is changed into an acid-like substance which has the same formula as damascenine but is capable of combining with bases. (See Arch. d. Pharm. 1901, 35.)

The barium compound of this new substance has the formula $(C_9H_{10}NO_3)_2Ba + C_9H_{11}NO_3$. The solution of the barium salt is precipitated by silver nitrate and lead acetate but not by copper acetate. The barium salt does not reduce Fehling's solution.

On acidulating the solution of the barium salt with acetic acid the same fluorescent substance was obtained which was described in aprevious paper (loc. cit.).

Barium permanganate oxidizes damascenine hydrochloride to oxalic acid with the formation of methylamine and ammonia. By chromic and sulphuric acids damascenine is decomposed into ammonia and some other products which could not be isolated in definite forms. The same was true when the alkaloid was heated with soda-lime or zinc dust. Arch. d. Pharm. 1904, 295.

O. Keller has investigated the action of bromine, acetyl chloride and acetic anhydride upon damascenine and the nature of the compound which is formed by internal rearrangement of the alkaloid when treated with alkalies. (See preceeding paragraph.) For the acid-like substance into which damascenine is converted by alkalies the name damascenine S is proposed.

The hydrochloride of damascenine was found to contain one molecule of water of crystallization. Upon heating to 90°—100° the hydrochloride loses both acid and base.

On adding bromine dissolved in absolute alcohol to a solution of damascenine in absolute alcohol a hydrobromide of dibromdamascenine, $C_9H_{11}Br_2NO_3.HBr$, was obtained. The hydrobromide is easily soluble in water, difficultly soluble in absolute alcohol and almost insoluble in ether. Melting point 198°—201°. Silver nitrate in aqueous solution precipitates all the bromine of the hydrobromic acid of the compound together with a small amount of the additive bromine.

Acethyl chloride or, better, acetic anhydride converts damascenine into a monoacetyl derivative, $C_9H_{10}(CH_3.CO)NO_3$. The acetyl compound crystallizes in plates or, needles melting at 203°—204°, is easily soluble in alcohol and difficultly soluble in water or ether.

The conversion of damascenine into damascenine S is best effected by adding potassium hydrate to a solution of damascenine hydrochloride in five times its amount of alcohol till the reaction is alkaline and then adding enough water to redissolve the potassium chloride which has separated out. The damascenine S crystallizes in

plates or prisms containing three molecules of water of crystallization and melting at 78°. Anhydrous the substance melts at 143°—144°. It is easily soluble in water or alcohol but difficultly soluble in ether, chloroform or ethyl acetate. The aqueous solution of damascenine S has an acid reaction and decomposes carbonates. The solutions in ether, alcohol or chloroform have a pretty blue fluorescence. The acid can be obtained directly anhydrous by recrystallizing it from a mixture of alcohol and chloroform. As a base it forms a hydrochloride, a sulphate and a platinum salt. It also forms a silver salt, $C_9H_{10}AgNO_3 + H_2O$, which is soluble in nitric acid and ammonia but insoluble in cold water. Hot water decomposes the silver salt.

A hydrochloride of the methyl ester of damascenine S, $C_9H_{10}(CH_3)NO_3.HCl + H_2O$, was obtained in hygroscopic needles, melting at 199°—200°.

By the action of bromine upon damascenine S a dibrom-addition compound was obtained which was different from dibromdamascenine showing that bromine does not cause the internal rearrangement of the alkaloid. On the other hand on converting damascenine S into a monoacetyl derivative by means of acetic anhydride the product was found to be identical with the acetyl compound obtained from damascenine under the same conditions. Hence in the acetylization the alkaloid is transformed into the acid-like substance.

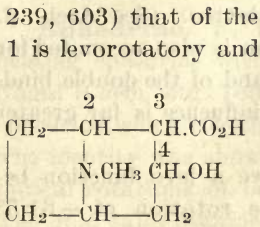
By the action of methyliodide both damascenine and damascenine S are converted into one and the same hydriodide of methyl damascenine, $C_9H_{10}(CH_3)NO_3.HI + H_2O$, showing that in this reaction too the alkaloid is changed to the acid. The free methyldamascenine was obtained from the hydriodide by means of sodium carbonate. From the methyldamascenine the iodomethylate, $C_9H_{10}(CH_3)NO_3.CH_3I$, was prepared by means of methyliodide in methylalcoholic solution.

A nitroso derivative of damascenine was prepared by the action of nitrous acid upon damascenine or damascenine S.

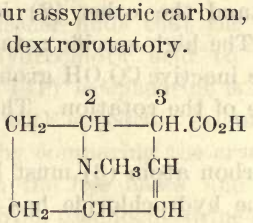
From various experiments the author draws the conclusion that there are in damascenine the groups $O.CH_3$, $NH.CH_3$ and $CO_2H$, so that the formula of the alkaloid can be resolved into $C_6H_3(O.CH_3).NH.CH_3.CO_2H$.

It would seem that damascenine is an N-methyl derivative of orthoanisidine carboxylic acid. Arch. d. Pharm. 1904, 299.

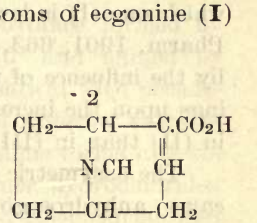
**Ecgonine.** J. Gadamer and T. Amenomiya continue their investigations of the optical functions of the assymetric carbon atoms of ecgonine. It was shown in a previous paper (Arch. d. Pharm. 239, 603) that of the four assymetric carbon, atoms of ecgonine (**I**) 1 is levorotatory and 2 dextrorotatory.



(I)



(II)



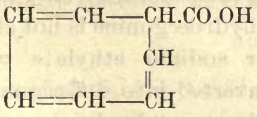
(III)

In the present paper it is shown that in l-ecgonine 3 and 4 must he levorotatory whereas in d-*ψ*-ecgonine 3 is levorotatory and 4 dextrorotatory.

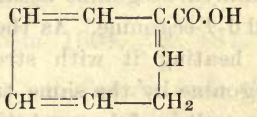
It was also found that anhydroecgonine must correspond to formula (II) containing three assymetric carbon atoms, not formula (III) with but two assymetric carbon atoms.

This formula for anhydroecgonine must be adopted on account of following considerations:

1. Einhorn and Tahara (Ber. Dtsch. Chem. Ges. 1893, 324) obtained from anhydroecgonine an acid which was shown by Willstätter to have the constitution of a cycloheptatriïn carboxylic acid. The formula of this acid must be either (IV) or (V) according to whether the formula of anhydroecgonine is (II) or (III). On treating this acid with alcoholic potassium hydrate it is transformed into two new compounds which are both isomeric with the acid and must differ from each other only in the position of the double binding



(IV)



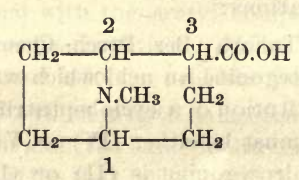
(V)

As in all such transformations the double bindings generally move towards the carboxyl group it is only (IV) which can give two isomers having the donble bindings nearer to the carboxyl group. Hence the acid must correspond to (II).

2. The high specific rotation of anhydroecgonine can be explained only by assigning to it formula (II) with three assymetric carbon atoms, not by (III) with only two assymetric carbon atoms of which one (I) is levo and the other (2) is dextro. (See Arch. d. Pharm. 1901, 663.) The high specific rotation is also accounted for by the influence of the inactive CO.OH group and of the double bindings upon the increase of the rotation. This influence is far greater in (II) than in (III).

The assymetric carbon atom (3) must have a levo function because anhydroecgonine hydrochloride has the rotation of $-61.5°$ and as (1) and (2) must nearly neutralize each other, having opposite rotations, the high negative rotation of anhydroecgonine can only be explained by assuming (3) to be levo and by the proximity of the "strengthening" group CO.OH to this (3) atom.

This assumption of the levo function of (3) is supported by the fact that, contrary to previous statements hydroecgonidine (VI) as found by the authors in slightly levorotatory. As in hydroecgonidine the "strengthening" CO.OH group is nearer the dextro atom (2) than the levo atom (I) hydroecgonidine ought to be dextrorotatory but as it is levorotatory this must be due to the levo function of (3).




Hydroecgonidine.

**(VI)**

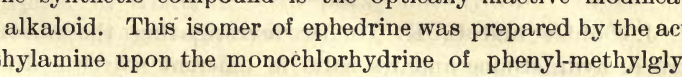
The function of the (3) atom in ecgonine must be the same as in anhydroecgonine because the latter is formed both from l-ecgonine and d-$\Psi$-ecgonine. As the rotation of anhydroecgonine is not changed by heating it with strong alkalies or sodium ethylate whereas l-ecgonine by the same treatment is converted into d-$\Psi$-ecgonine the conversion of l-ecgonine into d-$\Psi$-ecgonine must be due to a change in the function of the atom (4) not (3). Hence (3) must have a levo function in all ecgonine derivatives.

As to the function of the atom (4) it is elear that in l-ecgonine it must have a levo function as otherwise there is no explanation for the formation of d-$\Psi$-ecgonine from it; but in d-$\Psi$-ecgonine (d-ecgo-

nine) the atom (4) has most probably a dextro function and the rotation of this atom to the right in d-ecgonine is equal to the rotation of (4) to the left in l-ecgonine. Arch. d. Pharm. 1904, 1.

**Ephedrine.** F. Flaecher finds that the substance formed by heating ephedrine with hydrochloric acid to 170° and named by Nagai (Chem. Ztg. 1890, 441) isoephedrine is identical with pseudoephedrine which together with ephedrine exists in *Ephedra vulgaris.* The identity was shown by comparing the crystalline forms and the optical rotations of both the free bases and their hydrochlorides. The gold salts obtained from pseudoephedrine and isoephedrine were also found to be identical. Arch. d. Pharm. 1904, 380.

E. Fourneau has prepared several compounds that are isomeric with ephedrine, $C_{10}H_{15}NO$. Of these isomers one is in so many respects similar to the natural base that it is reasonable to assume that the synthetic compound is the optically inactive modification of the alkaloid. This isomer of ephedrine was prepared by the action of methylamine upon the monochlorhydrine of phenyl-methylglycol:



Monochlorhydrine of phenyl-methyl glycol. Methylamino-dimethyl-phenyl-carbinol.

The artificial base is a colorless liquid boiling at 145° under 24 mm. pressure, quite soluble in cold water, but insoluble in hot water. It slowly reduces potassium permanganate in acid solution and gives a silver mirror with silver oxide. The salts of the synthetic base could not be obtained in crystalline form.

Journ. Pharm, Chem. 1904, XX, 481.

**Euquinine,** $CO(O.C_2H_5)(O.C_{20}H_{23}ON_2)$. P. Cesaris finds that on mixing 3.96 grams of euquinine with 1.38 grams of salicylic acid dissolved in 100 c. c. of absolute alcohol a crystalline compound soon separates out which is colored green by hydrochloric acid, sulphuric acid and nitric acid and melts at 195°—196°. The compound is almost insoluble in cold water, a little more soluble in hot water, easily soluble in chloroform and hot alcohol and difficultly soluble

in ether, benzol or carbon disulphide. It is colored red by ferric chloride (reaction of salicylic acid) and olive green by chlorine water and ammonia (euquinine reaction). Boll. Chim. Farm. 1904, 11.

**Hydrastinine.** C. Liebermann and F. Kropf have prepared anhydrohydrastinine acetone by condensing hydrastinine with acetone. The reaction is the same as with cotarnine (see this Review page 160).

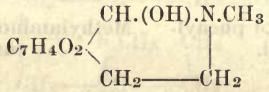
The anhydrohydrastinine acetone melts at a lower temperature (72°) than hydrastinine itself (116°—117°), and forms a hydrochloride and a platinum salt which were obtained by the same methods as the corresponding cotarnine compounds.

In the same way was obtained a condensation product of hydrastinine with acetophenone. The anhydrohydrastinine acetophenone is easily soluble in alcohol with fluorescence and crystallizes in prisms melting at 74°. It also forms a platinum salt.

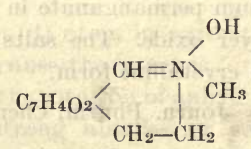
Ber. Dtsch. Chem. Ges. 1904, 214.

J. J. Dobbie and C. K. Tinkler investigating the absorption spectra of hydrastinine and its salts in different solvents draw the following conclusions in regard to the constitution of this base:

1. In the solid state or in solution in dry ether or chloroform hydrastinine is colorless and must be assumed to have the carbinol form.



2. In the colored aqueous or alcoholic solutions the alkaloid and its salts have the ammonium hydroxide form

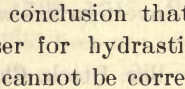


3. Dissolved in little alcohol the alkaloid exists in both forms, but the addition of much alcohol changes the colorless carbinol form completely to the colored ammonium form.

4. Alkalies added to the colored solutions of hydrastinine salts cause a reverse change from the ammonium form to the carbinol form.

The complete conversion of the amonium form into the carbinol form in solution by the addition of alkali can be noticed by the fact that the fluorescence of the solutions disappears completely when the transformation is complete.

The author draws the conclusion that the open chain aldehyde formula proposed by Roser for hydrastinine, not explaining these differences in the spectra, cannot be correct.



Roser's formula.

Journ. Chem. Soc. 1904, 1005.

**Isopilocarpine.** H. A. D. Jowett finds that upon melting isopilocarpine, $C_{11}H_{16}N_2O_2$, with patassium hydrate normal butyric acid is formed, not, as previously reported, isobutyric acid.

Proc. Chem. Soc. 1904, 14.

**Lupinidine.** R. Willstätter and W. Marx have investigated the composition and properties of lupinidine. The conclusions arrived at are as follows:

1. Lupinidine is identical with sparteine both alkaloids having the same formula, $C_{15}H_{26}N_2$, and agreeing also with regard to boiling point, specific gravity, solubilities etc.

2. The boiling point under 18 m. m. pressure is 180.5° and under 13 m. m. pressure 170.5°. The specific rotation in pure condition is $[\alpha]_D^{20°} = -5.96°$. Dissolved in 99% alcohol (C=14.206) the specific rotation is $[\alpha]_D^{20°} = -16.41°$.

3. Judging from the empirical formula and the behavior towards potassium permanganate there cannot be any double bindings in sparteine and the molecule must be made up of one aromatic ring or four saturated rings.

4. There are only three alkaloids present in the various lupinus plants: lupinine, $C_{10}H_{19}N_2$, in Lupinus luteus and Lupinus niger, sparteine, $C_{15}H_{26}N_2$ in Lupinus luteus and Lupinus niger, and lupanine $C_{15}H_{24}N_2O$ in Lupinus albus, Lupinus angustifolius and Lupinus perennis.

5. Sparteine is very difficultly volatilized with steam, has a very feeble odor, is easily soluble in benzol or ligroin and does not form a hydrate. On titrating sparteine with acids the amount of acid consumed varies with the concentration of the alkaloidal solution.

The statements of other investigators with regard to these points were found to be incorrect.

Ber. Dtsch. Chem. Ges. 1904, 2351.

**Lupinus Alkaloids.** According to E. Schmidt the alkaloids of Lupinus perennis consist chiefly of d-lupanine, $C_{15}H_{24}N_2O$, mixed sometimes with oxylupanine, $C_{15}H_{24}N_2O_2$, and sometimes with other alkaloids. Seeds obtained from the same source and apparently having the same morphological characteristics have yielded at different times different alkaloids.

On the suggestion of E. Schmidt some analyses and molecular weight estimations of lupinine were carried out by G. Fr. Bergh. The results obtained corroborated the statements of Willstätter and Fourneau with regard to this alkaloid (Arch. d. Pharm. 240, 335.)

Arch. d. Pharm. 1904, 409.

G. Fr. Bergh has investigated the alkaloids of Lupinus perennis. The alkaloids were obtained by the following method. The coarsely powdered seeds were extracted with water acidulated with hydrochloric acid, the liquid concentrated and the extract after making it alkaline with sodium hydroxide extracted first with ether and then with chloroform. In this way an ethereal and a chloroform extract were obtained which were worked up separately.

On distilling off the ether from the ethereal extract and treating the residue with a large amount of ether crystals of oxylupanine separated out on the walls of the vessel and a yellowish red sticky mass settled at the bottom. This mass could not be made to crystallize. From the ethereal mother liquor some d-lupanine was obtained.

The chloroform extract after distilling off the solvent was mixed with magnesium oxide, the mass thoroughly dried and then extracted for a month with ether in a Soxhlet apparatus. On distilling off the ether the residue was treated again with a large amount of cold ether which removed some d-lupanine and the remaining oxylupanine recrystallized from a mixture of acetone and water. From fifteen kg.

of the seeds 15 grams oxylupanine and 200 grams d-lupanine were obtained.

Oxylupanine, $C_{15}H_{24}N_2O_2 + 2H_2O$, forms colorless transparent rhombic prisms and melts air dried at 76°—77°; dried at 50°—60° in vacuum it melts at 172°—174°. When dried under ordinary pressure at 100° the alkaloid becomes brown. The specific rotation is + 64.12. The alkaloid forms a di- and a mono-hydrochloride. When the dihydrochloride is melted it is changed to the monohydrochloride. Oxylupanine also forms a hydriodide, a chloraurate and a chloroplatinate. The salts of oxylupanine crystallize less readily than those of d-lupanine.

The two alkaloids can be distinguished from each other by their behaviour with bromine water; with which d-lupanine gives a fine precipitate which on stirring disappears, whereas oxylupanine gives a flocculent amorphous precipitate which does not disappear on stirring.

Monoacetyl oxylupanine $C_{15}H_{23}N_2O_2(CH_3CO)$ was prepared by boiling oxylupanine with acetic anhydride. For analysis it was converted into its crystalline chloraurate.

Oxylupanine iodomethylate, $C_{15}H_{24}O_2N_2.CH_3I + H_2O$, was prepared by heating the alkaloid with excess of methyliode in methylalcoholic solution. After converting the iodomethylate into the chloromethylate the latter was converted into the gold and platinum salts.

On heating oxplupanine with red phosphorus and hydriodic acid it is converted into lupanine.

d-Lupanine forms a hydriodide which crystallizes with two molecules of water of crystallization. The salt cannot be dried under ordinary pressure without decomposition and loses its water of crystallization only when dried in vacuum to 100° for 24 hours. An iodomethylate was prepared by treating d-lupanine in methylalcoholic solution with methyliodide. From the mono-iodomethylate the corresponding gold and platinum salts were prepared.

Other bases could not be found in the seeds.

Arch. d. Pharm. 1904, 242.

**Morphine.** C. Reichard has found the following color reactions for morphine: On warming some morphine or its sulphate with a little sulphuric acid to which some sodium, arsenite sodium arsenate, antimony trichloride or stannous chloride had been added a perman-

ent red color is produced. Several other alkaloids tried did not give this reaction.

On adding a trace of morphine or any of its salts to a concentrated solution of bismuth chloride an intensely yellow color is produced. Many other alkaloids also give color reactions with bismuth chloride but these are more or less different from the morphine reaction. Atropine also gives a yellow color with bismuth chloride but the color disappears on warming the liquid.

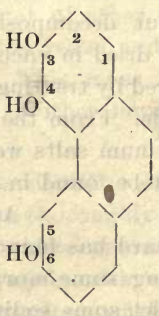
Cocaine gives no color reaction with bismuth chloride unless strong sulphuric acid be present but even then the color disappears on warming the liquid.

With a very dilute solution of cobalt nitrate, morphine gives no color whatever, but in presence of concentrated sulphuric acid a deep red or brown-red color is produced which slowly changes at first to a yellowish-red and then to a very permanent brownish-yellow.

Atropine gives with cobalt nitrate in the absence of strong sulphuric acid a grass green color.

With cerium dioxide (obtained by heating cerium nitrate) and sulphuric acid morphine gives on standing at ordinary temperature a blue violet color. Atropine and cocaine do not give the reaction. Brucine brought in contact with cerium dioxide and sulphuric acid in the cold gives a reddish or a reddish-yellow color which after a short while changes to an intense yellow. Chem. Ztg., 28, p. 1102.

L. Knorr continues his investigations on the constitution of morphine. It is known that the three alkaloids morphine, codeine and thebaine are derivatives of 3, 4, 6—trioxyphenanthrene (See this Review 1904 Prog. in Alk. Chem. during 1903)




Trioxyphenanthrene.

but the question about the form of linking and the function of the so called indifferent oxygen atom has not yet been cleared up.

We are also as yet in the dark with regard to the way in which the group—$CH_2.CH_2.N.CH_3$—which is eliminated from thebaine and codeinone in the form of ethanol methylamine, $HO.CH_2.CH_2.NH.CH_3$, by means of acetic anhydride is linked to the partially reduced phenanthrene nucleus.

The following experiments help to bring us nearer to the solution of these problems.

When $\alpha$-methylmorphimethine $(OH)(CH_3O)C_{17}H_{16}ON.CH_3$ is decomposed by means of hydrochloric acid (Ber. Dtsch. Chem. 27, 1147) there is formed among other products a basic substance $\beta$-chlorethyldimethylamine, $Cl.CH_2.CH_2.N(CH_3)_2$. The base itself could not be isolated but on distilling the basic part of the reaction products with sodium hydroxide compounds are obtained which are identical with those obtained by distillation with alkali of $\beta$-chlorethyldimethylamine made synthetically, namely, tetramethylethylenediamine, $(CH_3)_2N.CH_2.CH_2.N(CH_3)_2$, and ethanoldimethylamine, $OH.CH_2.CH_2.N(CH_3)_2$.

In order to separate these two bases the distillate is acidulated with hydrochloric acid and concentrated to a small bulk. On now adding absolute alcohol most of the hydrochloride of tetramethylethylenediamine is precipitated in small crystals. After separating these crystals by filtration the filtrate is treated with picric acid which precipitates the rest of the tetramethylethylenediamine as an insoluble picrate. The filtrate from this picrate is acidulated with sulphuric acid and the picric acid removed by shaking out the liquid with ether.

The liquid is now made alkaline with sodium hydroxide and the ethanoldimethylamine distilled over with steam into dilute hydrochloric acid. From the acid solution the ethanoldimethylamine is isolated in the form of its crystalline chloraurate.

On heating $\beta$-methylmorphimethine with alcoholic sodium ethylate to 150° the base is decomposed into methylmorphol and dimethylaminoethylether, $(CH_3)_2N.CH_2.CH_2O.CH_2.CH_3$. A small amount of dimethylamine is also formed at the same time. As $\alpha$-methylmorphimethine is converted into the isomeric $\beta$-modification by the

action of sodium ethylate and codeine iodomethylate is changed by the same reagent into α-methylmorphimethine we can use for the preparation of the dimethylaminoethylether either one of the two methylmorphimethines or codeine iodomethylate.

The dimethylaminoethylether is an oily liquid which can be freed from water by means of potassium hydroxide and boiling with barium oxide. It forms a chloraurate, a picrate and an iodomethylate, $(CH_3)_3I.N.C_2H_4O.C_2H_5$, (ethylether of cholinehydriodide).

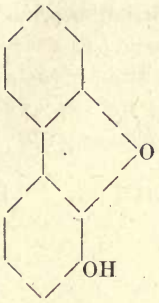
On heating, thebaine iodomethylate with sodium ethylate for a few minutes thebaol (dioxyphenanthrene dimethyl ether) and tetramethylethylenediamine are formed. More prolonged heating resinifies the subsance.

This decomposition of thebaine iodomethylate can also be effected by heating it with alcohol alone to 160°—165°, but under these conditions dimethylamine is also formed. Similar decomposition products are formed by heating codeinone iodomethylate under pressure with alcohol, only instead of thebaol, 3, —methoxy—4, 6—dioxyphenanthrene is produced.

This easy decomposition of the iodomethylates of thebaine and codeinone shows that the side chain C.C.N, in these substances is easily split off. The greater stability of codeinone iodomethylate is due to the fact that codeine contains a tetrahydrophenanthrene ring whereas in thebaine there is a dihydrophenanthrene ring.

It is evident that the dimethylaminoethylether is not a primary product in the above reaction. It could not also be formed from ethanoldimethylamine because hydramines cannot be converted into ethers by alcohol or sodium ethylate. We must therefore suppose that the chain C.C.N is split off as an unsaturated vinyldimethylamine, $(CH_3)_2N.CH:CH_2$, group. Such a group could be easily converted by the action of alcohol into dimethylaminoethylether, by the action of acetic anhydride into the acetate of dimethylaminoethanol and in the presence of dimetylamine into tetramethylethylenediamine.

If this supposition should prove to be correct the formula of morphine will have to be changed so as to show that the indifferent oxygen atom is not a member of an oxazine ring as is generally supposed but is linked in the same way as in morphenol.




Morphenol.

With regard to the C.C.N group we would have to assume that it is present in morphine in the form of a reduced pyrroline ring or a reduced pyridine ring.

It would of course be difficult to account for the great facility with which this ring complex is split off from the molecule unless we assume that the paradihydro system behaves somewhat like quinones in which the groups generally have great mobility.

Ber. Dtsch. Chem. Ges. 1904, 3494.

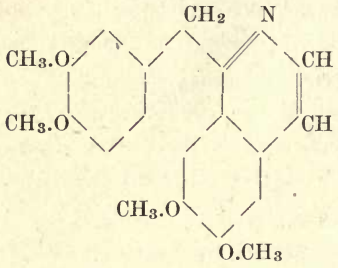
**Nicotine.** C. S. Hudson has investigated the miscibility of nicotine with water at different temperatures.

The conctraction and evolution of heat which take place upon mixing nicotine with water and the dependence of the specific rotation and the refraction equivalent of the alkaloid upon the concentration of its solution seem to indicate the formation of a hydrate. The formation of such a hydrate would also explain why nicotine is miscible with water in all proportions only at certain temperatures. Below 60° and above 210° nicotine and water are miscible with each other in all proportions. Solutions containing less than 7.8 per cent or more than 82 per cent of nicotine remain homogeneous at all temperatures. A solution containiug 7.8 percent nicotine becomes turbid at 89° and clear again at 150°. Below 90° the upper layer is richer in water, above 90° the lower layer is richer in water and at 90° the two layers interchange places.

Zeitschr. phys. Chem. 47, 113.

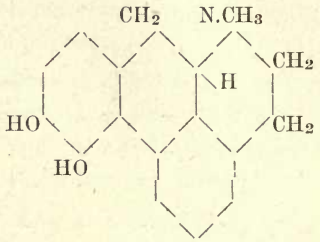
**Papaverine.** R. Pschorr in collaboration with M. Stählin and M. Silberbach have succeeded in converting papaverine into an isoquinoline derivative of phenanthrene which is very nearly related to apomorphine.

The relationship between papaverine and apomorphine is shown by their structural formulae:




Papaverine

(I)




Apomorphine

(II)

It seemed, therefore, possible to convert amidopapaverine into a derivative of apomorphine by the same method by which ortho-amidostilbene derivatives are converted into phenanthrene derivatives, i. e., by converting the amido into a diazo compound and then condensing the two benzol rings of the molecule through the elimination of the the $NH_2$ group:

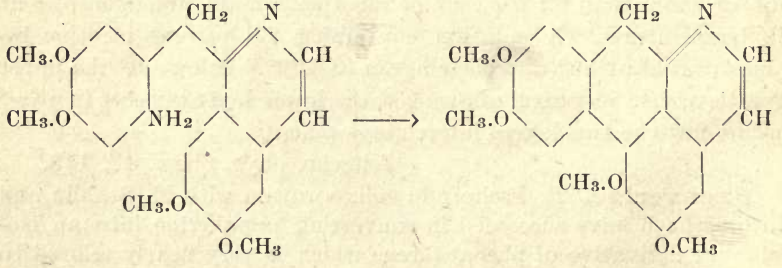

Orthoamidostilbene

(III)

Phenanthrene

(IV)

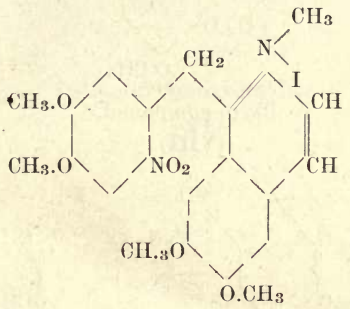
Hence an attempt was made to convert orthoamidopapaverine into an isoquinoline derivative of phenanthrene by eliminating the amido group and condensing the two benzol rings of the molecule




Orthoamidopapaverine.

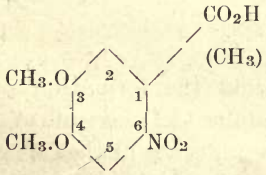
Isoquinoline derivative of phenanthrene.

The orthoamidopapaverine pas prepared from orthonitropapaverine in which the orthoposition of the nitro group was proven by the fact that upon oxidation of its iodomethylate (V) it gave symmetrical nitroveratric acid (VI) and by treatment with alkali it gave 6-nitro-3, 4-dimethoxytoluol (VI) and 6, 7-dimethoxy-N-methylisoquinoline (VII).



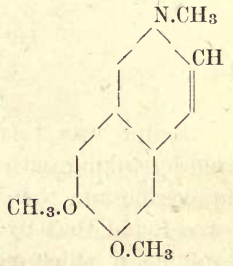

Orthonitropapaverineiodomethylate.

**(V)**




Symemtrical nitroveratric acid and 6-nitro-3, 4-dimethoxytoluol.

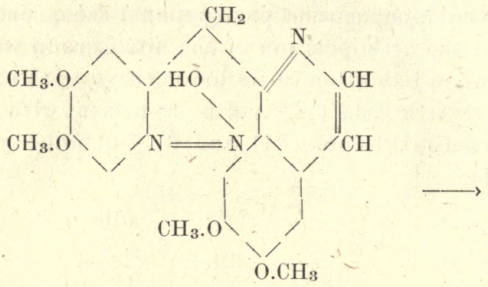
**(VI)**




6, 7-Dimethoxy-N-methylisoquinoline.

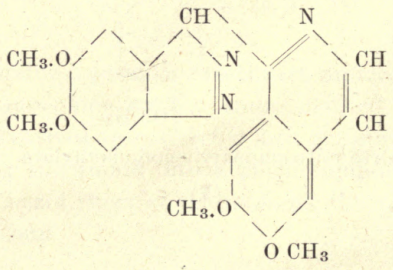
**(VII)**

The reduction of the ortho-nitropapaverine to the corresponding amido derivative presented no difficulties but it was found impossible to eliminate the amido group and thus condense the two benzol rings of the molecule by diazotizing the amido compound and then boiling the diazo compound with powdered copper. It would seem that the diazo compound easily loses the elements of water and is converted into an anhydride from which the nitrogen atom cannot be split off



Diazo compound.

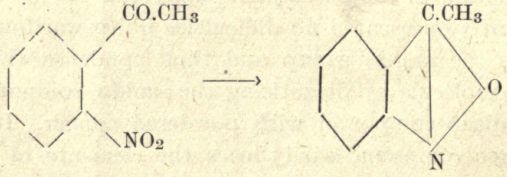
**(VIII)**



Anhydride.

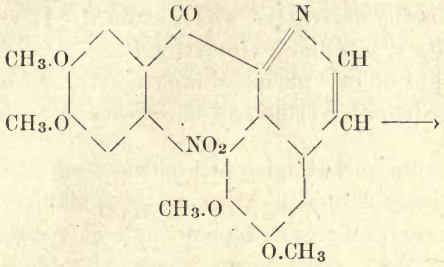
**(IX)**

An attempt was then made to avoid the formation of this anhydride by taking orthonitropapaveraldine (XI) instead of orthonitropapaverine and thus eliminating the influence of the $CH_2$ group. But it was found that by reduction in acid solution of orthonitropapaveraldine a substance was formed which had the formula $C_{20}H_{18}N_2O_5$ and showed neither the reactions of a ketone nor those of a primary amine. It is probable that the reduction takes place in the same way as in the formation of methylanthranil (X) from orthonitroacetophenone.



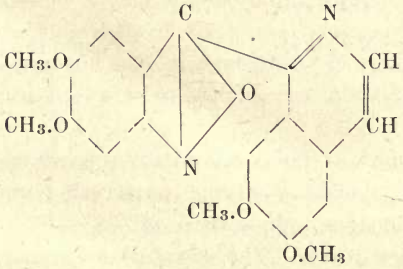
O.Nitroacetophenone. Methylanthranil.

**(X)**



Orthonitropapaveraldine.

**(XI)**



Anthranilopapaverine.

**(XII)**

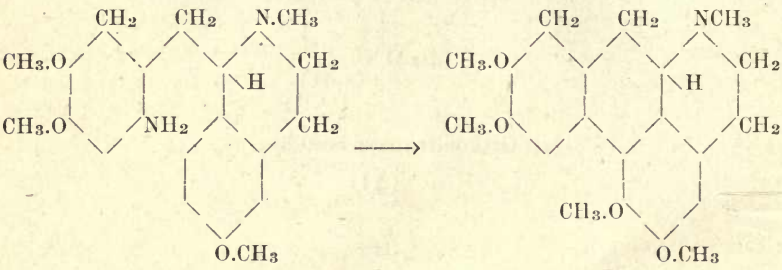
The substance was therefore named anthranilopapaverine.

If the reduction of o.nitropapaveraldine be carried out by means of ammoniumsulphide the reaction takes a normal direction and o.amidopapaveraldine is obtained. But on trying to diazotize the amido compound and then split off the diazo group it was found impossible to isolate a definite compound. Though the product obtained by boiling the diazo compound with water was crystalline it was almost perfectly black and could not be purified.

After these unsuccessful attempts the formation of a phenanthrene derivative of isoquinoline was at last accomplished by starting with o.amidotetrahydro-N-methylpapaverine. On reducing o.nitropapaverine chloromethylate both the nitro group and the isoquinoline complex of the molecule are reduced with the formation of o-amidotetrahydro-N-methylpapaverine. On diazotizing this amidocompound and then treating with powdered copper in the cold the

desired phenanthrene derivative was obtained. It was characterized in the form of its crystalline iodomethylate.

The formation of the phenanthrene derivative from the amido-N-methyltetrahydropapaverine can be expressed as follows:



O.Amido-tetrahydro-N-methyl-papaverine.

**(XIII)**

Phenanthreno-N-methyl-tetrahydropapaverine.

**(XIV)**

Experimental. — The orthonitropapaverine was obtained in almost theoretical yield by adding papaverine under constant stirring to nitric acid at a temperature of —5° —0° and then throwing the liquid into ice water. The crystalline nitrate of o.nitropapaverine thus obtained is warmed with ammonia on the waterbath till the whole mass is converted into the free base.

On treating the o.nitropapaverine with methyliodide in chloroformic solution at 100° the iodomethylate was obtained. In the same way the bromomethylate can be made substituting methylbromide for methyliodide.

For the preparation of the chloromethylate of o.nitropapaverine the latter was converted into the methylsulphate-methylate, $C_{20}H_{20}O_6N_2\langle^{CH_3}_{CH_3SO_4}$, by means of dimethylsulphate in chloroformic solution and then decomposing the quaternary methylsulphate methylate in hot concentrated aqueous solution with a strong solution of potassium chloride. By substituting potassium iodide or potassium bromide for pocassium chloride the above mentioned iodomethylate and chloromethylate of o.nitropapaverine can be obtained.

On oxidizing the iodomethylate of o.nitropapaverine with hot potassium permanganate symmetrical 6-nitroveratric acid (VI) was formed.

On warming the iodomethylate with potassium hydrate 6-nitro-3, 4-dimethoxytoluol (VI) separated out. From the mother liquor of the latter 6, 7-dimethoxy-N-methylisoquinoline (VII) was obtained by adding strong hydrochloric acid in which the isoquinoline derivative is difficultly soluble.

The orthoamidopapaverine was prepared by reducing the o.nitropapaverine ia alcoholic solution witth stannous chloride dissolved in strong hydrochloric acid and precipitating the amine with excess of alkali. The o.amidopapaverine crystallizes with one molecule of alcohol of crystallization which is partially given off at ordinary temperature.

The amidopapaverine was diazotized in the usual way but the solution soon deposited a yellow gelatinous mass without evolution of nitrogen. From the salt of the diazo compound the free base was liberated by ammonia and recrystallized from alcohol. The substance was undoubtedly the anhydride of diazopapaverine corresponding to formula (IX).

If the freshly prepared solution of the diazopapaverine be treated in the cold with powdered copper nitrogen is evolved and the liquid assumes a red color. From the red liquid ammonia precipitates a red amorphous substance which could not be purified.

An iodomethylate of the diazopapaverine was prepared by means of methyliodide in chloroformic solution at 100°. The iodomethylate contains one molecule of water of crystallization which it loses only when heated in vacuum.

The methylsulphate methylate of diazopapaverine is formed on digesting diazopapaverine with dimethylsulphate in chloroformic solution and precipitating the methylsulphate methylate with ether.

Potassium iodide in hot concentrated solution converts the methylsulphate methylate into the above mentioned iodomethylate of diazopapaverine.

Unlike the iodomethylate of nitropapaverine (V) the iodomethylate of diazopapaverine is not decomposed by warm potassium hydrate but there is simply a replacement of the halogen atom by an OH group.

Orthonitropapaveraldine was prepared by two different methods: either by nitrating papaveraldine or by oxidizing nitropapaverine. The papaveraldine was prepared by oxidizing papaverine with

potassium dichromate in glacial acetic acid solution and purified by solution in benzol and precipitation with petroleum ether.

On treating papaveraldine with nitric acid and throwing the liquid into water the nitrate of o.nitropapaveraldine is precipitated.

The same compound was obtained by oxidizing o.nitropapaverine with sodium dichromate in boiling glacial acetic acid.

The reduction of o.nitropapaveraldine obtained by either of the above methods to anthranilopapaverine (XII) was carried out by means of stannous chloride and hydrochloric acid in alcoholic solution. The substance shows neither the reactions of a ketone nor those of an amine.

If the reduction of o.nitropapaveraldine be effected by passing a current of sulphuretted hydrogen into a boiling alcoholic solution of the nitro compound in presence of ammonia the reduction takes a normal direction and o.amidopapaveraldine is formed. The latter was purified by solution in hydrochloric acid and precipitation with ammonia.

An attempt to diazotize the o.amidopapaveraldine in presence of strong sulphuric acid resulted in the formation of a sulphonic acid, $C_{20}H_{18}O_8N_2S$.

Orthoamidopapaveraldine was found to form two series of salts: With very dilute acids intensily red solutions are obtained but with strong acids the solutions are yellowish-green and become red upon addition of water.

On diazotizing the o.amidopapaveraldine a substance was obtained which evolves nitrogen at 60° with the formation of black needle shaped crystals which could not be purified.

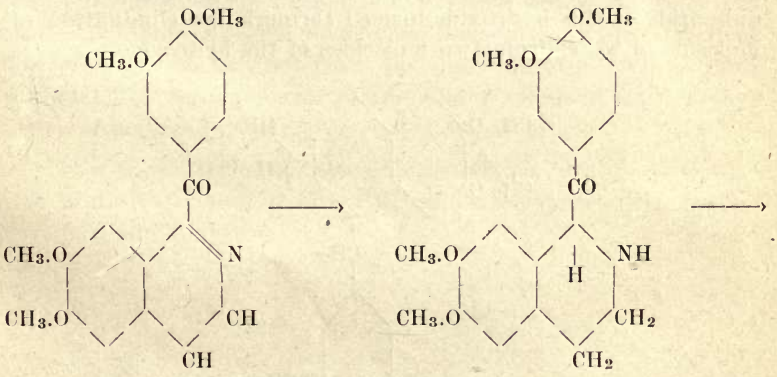
On reducing tne chloromethylate of nitropapaverine with tin and hydrochloric acid the tin double salt of amidopapaverine is formed at first but on boiling the liquid for two hours the compound is further reduced and the tin double salt of N-methyltetrahydroamidopapaverine (XIII) separates out. The double salt was decomposed by means of sulphuretted hydrogen, the excess of $H_2S$ removed by a current of air and, after adding some sodium sulphite (to prevent oxidation), the N-methyltetrahydropapaverine precipitated with a saturated solution of potassium carbonate.

The compound forms soluble salts with hydrochloric, sulphuric and nitric acids and reduces silver nitrate solutions even in the cold.

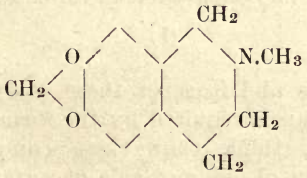
The preparation of the looked for phenanthrene derivative

(XIV) was carried out by diazotizing the N-methyltetrahydropapaverine in presence of dilute sulphuric acid and heating the resulting sulphate of the diazo compound with powdered copper. When the evolution of nitrogen ceased the phenanthreno-N-methyltetrahydropapaverine (XIV) was precipitated by ammonia in a semisolid condition. On dissolving the phenanthrene derivative in chloroform and evaporating off the solvent the compound was left in the form of a reddish-brown syrupy liquid which could not be made to crystallize. It was analyzed after converting it into the crystalline iodomethylate by means of methyliodide in alcoholic solution. Ber. Dtsch. Chem. Ges. 1904, 1927.

M. Freund and H. Beck have tried to reduce papaveraldine in the expectation that after taking up four atoms of hydrogen papaveraldine could be converted by means of methylation and then splitting off the dimethoxybenzoyl group into a substance similar to hydrohydrastinine or hydrocotarnine




Papaveraldine or tetramethoxybenzoylisoquinoline.




Hydrohydrastinine.

It was found that on reducing papaveraldine electrolytically the substance took up six instead of four atoms of hydrogen one atom of oxygen going out at the same time as water. The new compound is isomeric but not identical with tetrahydropapaverine. It was therefore named isotetrahydropapaverine. It has the formula $C_{20}H_{25}NO_4$ or possibly $(C_{20}H_{24}NO_4)_2$ and could not be obtained in crystalline form. It was purified by converting it into its nitroso derivative. It forms a hydrochloride and a hydriodide.

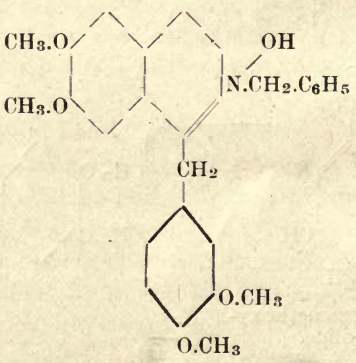
On heating the nitroso derivative with alcoholic hydrochloric acid it was reconverted into isotetrahydropapaverine.

With methyliodide the base gave a compound which seemed to be the hydriodide of methylisotetrahydropapaverine.

The physiological effect of the hydrochloride of the base is similar to that of cocaine. Ber. Dtsch. Chem. Ges. 1904, 3321.

H. Decker and O. Klauser have investigated the constitution of the alkylhalides of papaverine.

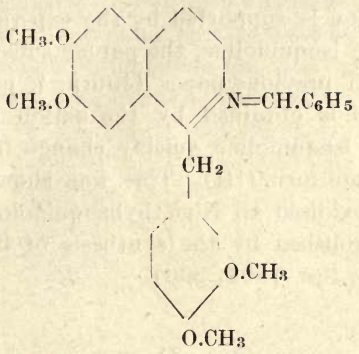
By the action of alkali upon these alkylhalides Stransky (Monatshefte f. Chem. 1888, 751) obtained compounds which he considered to be derivatives either of papaverinium hydroxide (I) or of the anhydride of this hydroxide formed through the elimination of one molecule of water from two molecules of the hydroxide




N-Benzylpapaveriniumhydroxide.

(I)

According to Claus and Kassner these compounds contain one molecule water less than is required by the formulae of the hydroxides. They, therefore, think that these compounds are derived through the elimination of one molecule of water from one molecule of the hydroxide with the formation of alkylidene compounds (II)

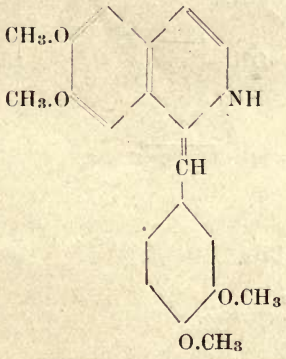



Benzylidenepapaverine.

**(II)**

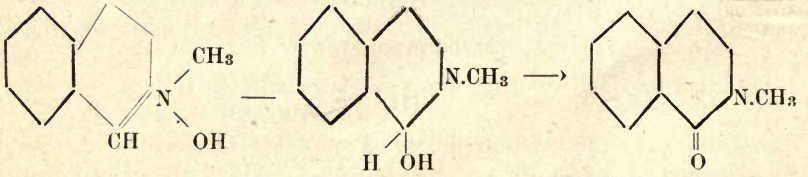
The authors find that in accord with Claus' statement these ether soluble compounds really contain one molecule water less than the corresponding papaverinium hydroxide derivatives and that they are derived not from two but from one molecule of the base. This was shown by an estimation of the molecular weight of the N-methyl derivative of papaverine (V).

As to the constitution of these compounds the authors consider them to be derivatives of a hypothetical base isomeric with papaverine named isopapaverine




Isopapaverine.

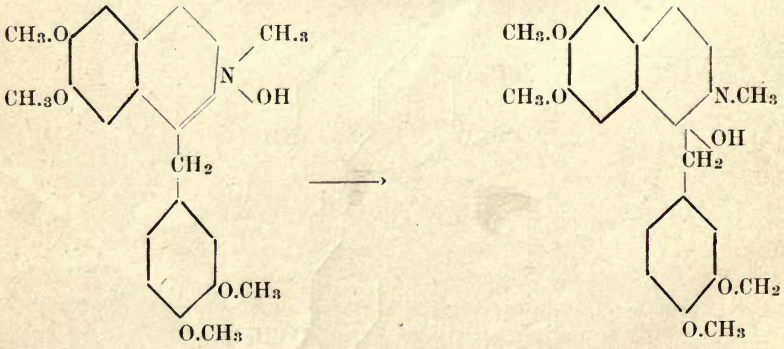
This supposition is supported by the experience of the authors with derivatives of isoquinoline, the parent substance of papaverine. It was shown in a previous paper (Journ. f. pr. Chem., 1893, 38) that the compounds obtained by the action of alkali upon the iodomethylate of isoquinoline quickly change from the ammonium form to the carbinol form (III). This was shown by the fact that the base can be oxidized to N-methylisoquinolone (IV) whose constitution was established by the synthesis of Bamberger and Frew (Ber. Dtsch. Chem. Ges. 1894, 206)




Ammonium base. Carbinol form. N-Methylisoquinolone.

(III) (IV)

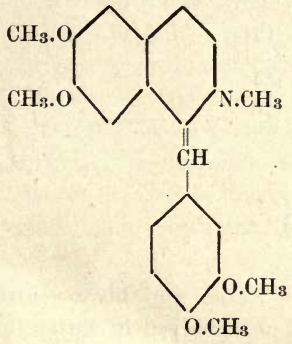
In the same way the ammonium form of alkyl papaverine (V) which is formed at first is supposed to be transformed into the car binol form (VI) in the next step




Ammonium base. Carbinol base.

(V) (VI)

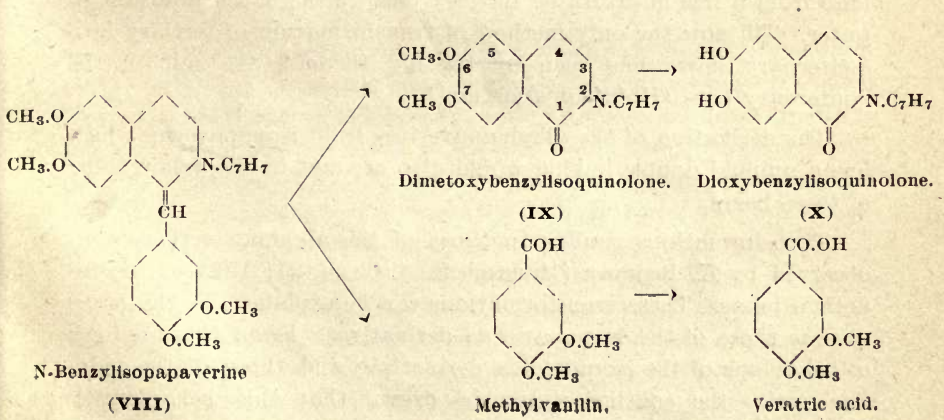
As these carbinol bases of papaverine are tertiary, not secondary like the isoquinoline compounds, the papaverine bases cannot be changed into isoquinolone compounds but are transformed into isopapaverine derivatives, i. e., (VI) changes to (VII).




N-methylisopapaverine.

**(VII)**

The correctness of this view was shown by the fact that N-benzylisopapaverine can be oxidized to a derivative of N-benzylisoquinolone. The oxidation takes place according the following scheme:




N-Benzylisopapaverine
**(VIII)**

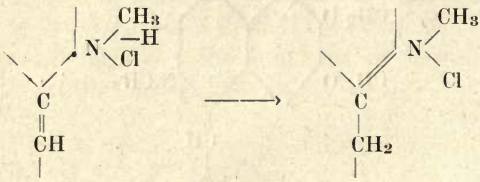
Dimetoxybenzylisoquinolone.
**(IX)**

Dioxybenzylisoquinolone.
**(X)**

Methylvanilin.

Veratric acid.

The reconversion of the tertiary alkylisopapaverines into salts of quaternary papaverinium bases by means of acids can be explained by assuming that at first a salt of the tertiary base is formed which soon changes to a salt of the quaternary papaverinium base, i. e., the grouping (XI) changes to the grouping (XII)



(XI) (XII)

The observation of Claus and his co-workers that the yellow alkylisopapaverines when dissolved in water form colorless, strongly alkaline solutions of papaverinium hydroxides (VII ——› V) from which upon concentration the isopapaverines again separate out (V ——› VII) can be explained by assuming that this reversible transformation is either of the same nature as the formation of salts (XI ——› XII) or that there is at first an addition of the elements of water to the double binding with the formation of the carbinol base (VIII ——› VI) which then changes to the ammonium form (VI ——› V).

We have here then a new case of formation of a free quaternary base from a free unsaturated tertiary base through the addition of water. Till now the only method of transformation of tertiary into quaternary bases has been by passing through the salt of the quaternary base (Hofmann's method).

The derivation of the alkylpapaverines from isopapaverine which has a quinoid double linking would also account for the yellow color of these bases.

Transformations similar to those of the alkylpapaverines were observed by K. Brunner (Monatshefte f. Chem. 21, 156) in the indolium bases. These transformations can be explained in the same way as those of the isopapaverine derivatives. From this analogy of behaviour of the isoquinoline derivatives and those of the indoline series the conclusion can be drawn that this behaviour is

characteristic of all cyclo-ammonium bases having an alkyl substitution group in $\alpha$-position.

Experimental. N-Methylisopapaverine (VII) was prepared by heating papaverine with methyliodide to 100° for six hours and recrystallizing the iodomethylate thus obtained from water. The free N-methylisopapaverine can be obtained from this iodomethylate by adding alkali to its aqueons solution.

If to a dilute solution of the iodomethylate (0.6%) a few drops of alkali be added and the liquid shaken up with benzol the latter assumes a yellow color. On adding more alkali the aqueous liquid also becomes yellow and when the amount of alkali reaches 15 to 18 per cent a thick yellow crystalline precipitate of N-methylisopapaverine is formed which disappears again upon addition of water the liquid becoming colorless.

This yellow precipitate is not pure N-methylisopapaverine but contains some unchanged iodomethylate and probably also some of the carbinol base (VI). The N-methylisopapaverine can be purified by dissolving it in water and precipitating with a 30% solution of sodiumhydroxide. It forms yellow transparent crystals melting at 129°—131°. It is deliquescent in the air absorbing carbon dioxide and water. The aqueous solution of N-methylisopapaverine is colorless and has a strong alkaline reaction. Upon concentration of the solution or addition of alkali the yellow isopapaverine base is precipitated. Acids convert the isopapaverine base quantitatively into salts of methylpapaverine. Picric acid converrs the N-methylisopapaverine into a picrate which is identical with N-methylpapaverine picrate (XI to XII).

An ethylisopapaverine was obtained which is even less stable and more deliquescent than the methyl compound. With even very little water the ethyl compound forms a yellow caustic solution of ethylpapaveriniumhydroxide from which the yellow isopapaverine is reprecipitated upon the addition of alkali or concentration of the liquid. From a benzol solution of the isobase the ammonium base can be removed by shaking with water.

Quantitative titrimetric estimations of the partition of the base between benzol and water showed that with the increase of the dilution of the aqueous solution the ratio of the amounts taken up by the two immiscible solvents increases in favor of the water. For this reason the presence of alkali which diminishes the number of ious

and the tendency of formation of hydrates displaces the quotient in the opposite direction, i. e., in favor of the benzol.

N-Benzylisopapaverine (VIII) is obtained more easily than the methyl compounds. Even the addition of only two and a half per cent of sodium hydroxide to a solution of papaverine benzylchloride precipitates the yellow isobase in crystalline form and once formed the isobase is only slowly reconverted into the ammonium base by water. It would seem that with the increase in the molecular weight of the N-substitution groups the equilibrium is displaced in favor of the isobase. Hence while methylisopapaverine is alkaline even to phenolphtaleïn, benzylisopapaverine is alkaline only towards litmus but not towards phenolphtaleïn.

N-Benzylisopapaverine shows the phenomenon of auto-oxidation with the intermediate formation of superoxides as oxygen carriers. On passing air through a one per cent solution of the benzyl compound in presence of a small amount of alkali the odor of methylvanilin is developed, and after a few days about 90% of the theoretical amount of 6, 7-dimethoxy-N-benzyl-1-isoquinolone is formed (VIII ——› IX). In the mother liquor small amounts of veratric acid can be found.

The dimethoxybenzylisoquinolone forms an orange-red picrate which upon recrystallization from alcohol is decomposed into its components coloring the solution yellow. The picrate is probably not a salt of the tertiary base but simply a moleculor addition compound in which the picric acid is attached to the benzol ring.

By means of hydrochloric acid the dimethoxybenzylisoquinolone was converted into the corresponding dioxy compound (1X ——›X). The free dioxybase was obtained by passing carbon dioxide into its alkaline solution. The base gives no color reactions with ferric chloride. From dilute solutions in alkalies the alkaline salts are precipitated by concentrated alkalies.

The methyl and ethylisopapaverine are also capable of auto-oxidation. Ber. Dtsch. Chem. Ges. 1904, 520.

H. Decker and his collaborators have prepared several derivatives of isopapaverine (see preceeding paragraph). Some of these are derived from isopapaverine itself while others are derivatives of monobromisopapaverine. The isopapaverine derivatives were obtained by the action of alkalies upon the corresponding papaverinium compounds:

1. Quaternary papaverinium salts. — Papaverine n-butylbromide, $C_{24}H_{30}O_4NBr$, was prepared from its components by heating them to 100° for 12 hours. It is a crystalline powder containing two molecules of water of crystallization. It melts first at 109°, then becomes solid on further heating and decomposes at 217°.

Alkalies convert the n-butylbromide compound into n-butyl-iso-papaverine which has a yellow color and is difficult to crystallize. Hydrochloric acid converts the n-butylisopapaverine into papaverinium chlorobutylate from which were obtained a picrate, a mercury salt and a chloroplatinate.

Papaverine iodoisobutylate, $C_{24}H_{30}O_4NI$, was prepared by the same method as preceeding compound. From its solutions alkalies precipitate the corresponding yellow isobase.

Papaverine-para-nitrobenzylchloride, $C_{27}H_{27}O_6N_2Cl$, was obtained by heating the components to 140° for six hours in an open vessel, then dissolving the product in alcohol and precipitating it with ether. It is difficultly soluble in water and forms a picrate and a mercury salt.

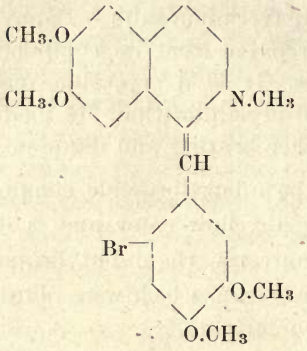
Addition of alkali to this paranitrobase does not liberate the isobase but the alkaline liquid soon assumes a red eolor which after a while changes to black indicating a deeper decomposition. The same reaction is produced even by ammonia.

A papaverine iodoisopropylate could be obtained only in small amount and with great difficulty.

2. Monobrompapaverine, $C_{20}H_{20}O_4NBr$, was prepared by adding bromine with constant stirring to a mixture of papaverine and strong hydrochloric acid. It forms small needles easily soluble in water. Dilute alkalies do not split off hydrobromic acid from the brom-papaverine showing that the bromine atom is not attached to the methylene group of the alkaloid.

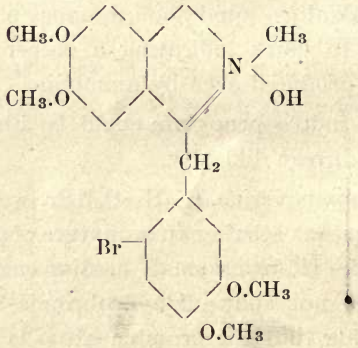
On heating brompapaverine with methyliodide N-methylbrom-papaveriniumiodide was obtained.

Treated with dimethylsulphate brompapaverine gives an addition compound which is converted by sodiumhydroxide into N-methyl-bromisopapaverine (I)



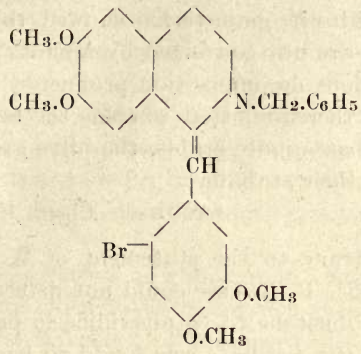

(I)

This brominated isopapaverine base is much more stable than the corresponding nonbrominated isopapaverine, The brominated compound reacts only slowly with waterforming brompapaverinium methylhydroxide (II).




(II)

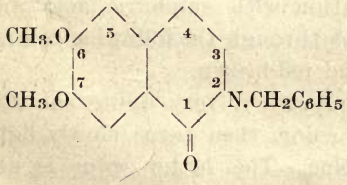
When brompapaverine is heated with benzylchloride to 120°—130° for four hours an addition compound is formed which is converted by sodiumhydroxide into N.benzylbromisopapaverine (III)



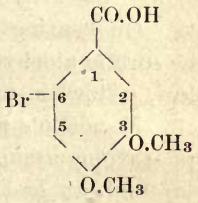

**(III)**

The brominated benzylisopapaverine base is also much more stable than the corresponding nonbrominated compound.

The N-Benzylbromisopapaverine base is only slowly affected by the oxygen of the air, but potassium permanganate (½%) quickly oxidizes it to N-benzyl-6, 7-dimethoxy-α-isoquinolone (IV) and 6-bromveratric acid (V)

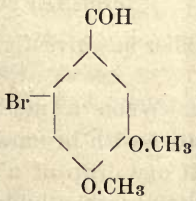



**(IV)**




**(V)**

If less potassium permanganate be taken in this reaction there seems to be formed instead of the bromveratric acid 6-bromveratric aldehyde (VI)




**(VI)**

Experiments with nitropapaverine showed that the alkylhalides of nitropapaverine are not converted by alkalies into isopapaverine bases but into various decomposition products.

It would seem, therefore, that whereas the bromine atom makes the isopapaverine bases more stable, the nitro group to the contrary greatly diminishes their stability.

Ber. Dtsch. Chem. Ges. 1904, 3809.

**Pepper.** Contrary to the statement of W. Johnstone (Chem. News 1888, 58, 235), R. Kayser could not detect any volatile alkaloid supposed by Johnstone to be piperidine in pepper. On distilling pepper with steam the distillate was found to be perfectly neutral.

On distilling pepper with magnesium oxide some ammonia was formed which was identified by the properties of the hydrochloride and the chloroplatinate. Zeitschr. öffentl. Chem. 1904, 137.

**Pilocarpine.** Et. Barrall describes some new color reactions of pilocarpine:

1. On heating pilocarpine with a solution of sodium persulphate the liquid becomes yellow, emits a narcotic and slightly ammoniacal odor and blackens mercurous nitrate.

2. On heating a pilocarpine solution with sulphuric acid and some formic aldehyde the liquid passes through the following colors: yellow, yellowish, brown, blood-red and red-brown.

3. Mandelin's reagent when heated with a very dilute solution of pilocarpine assumes first a yellow color, then turns slowly light green and at last becomes light blue. The latter color is not changed by dilution with water.

4. On heating a solution of pilocarpine with a one per cent solution of potassium permanganate in sulphuric acid the liquid at first becomes colorless and then assumes a dark yellow tint emitting an odor resembling that of burned sugar.

Journ. Pharm. Chim. XIX, 188.

**Quinine.** J. B. Ballandier has investigated some color reactions of some alkaloids.

Quinine and Quinidine. When a moderately acid solution of quinine or quinidine is treated with bromine vapors the fluorescence of the liquid disappears. If one drop of a copper sulphate solution and one drop ammonia water be then added to the liquid the latter assumes a peach flower color which on adding more ammonia

changes first to violet and then to green. If acid be now added to the liquid the color becomes either blue or violet according to the amount of acid added.

On adding ammonia alone to a solution of quinine previously treated with bromine vapors the thalleioquin reaction is developed. If to the liquid be then added a drop of a copper sulphate solution the liquid assumes a dark blue color which is not destroyed by excess of mineral acids.

CHELIDONINE. A solution of guajacol in conceütrated sulphuric acid gives a beautiful carmine-red color with chelidonine.

CHELIDONINE AND NARCEINE. Tannin-sulphuric acid gives a green color with chelidonine and narceine.

Journ. Pharm. Chim. 20, 151.

E. Léger has investigated André's reaction for quinine which consists in treating the solution of a quinine salt successively with chlorine water or bromine water and ammonia. The author finds that the color obtained varies with the amount of bromine and water added. In some cases the liquid even remains colorless. It is therefore necessary to carry out the reaction always under the same conditions.

Working under definite conditions it is even possible to apply André's reaction to the quantitative evaluation of cinchona bark.

Journ. Pharm. Chim., XIX, 281.

Further work by E. Léger upon André's reaction for quinine (see preceeding paragraph) has shown that the reaction cannot be made use of for the quantitative evaluation of cinchona bark.

Journ. Pharm. Chim. XIX, 434.

H. Carette has investigated the composition of several neutral hydrochlorides of quinine.

1. A neutral hydrochloride containing two and a half molecules of water of crystallization.

This was obtained by dissolving one molecule of anhydrous quinine in two molecules hydrochloric acid largely diluted with water and concentrating the liquid on the waterbath.

This hydrochloride forms fine radiated crystals which begin to melt at 80°, become brown at 215° and melt to black liquid at a higher temperature.

The salt is hygroscopic but does not liquify unless exposed to a very moist atmosphere. In dry air at a temperature of 20° the

crystals lose a small part of their water of crystallization. At 102° all the water of crystallization is removed the salt assuming a yellowish tint which disappears on cooling. There is no loss of hydrochloric acid at this temperature.

2. A neutral hydrochloride containing one and a half molecules of alcohol of crystallization. This salt is obtained by recrystallizing neutral quinine hydrochloride from an alcoholic solvent containing either 30, 55 or 95 per cent alcohol.

The salt forms large transparent crystals which become yellow at 165°—170° and liquid at 180°—185°. The alcohol is almost completely removed on keeping the salt in vacuum at ordinary temperature.

The dry salt assumes a yellowish tint on exposure to light. The crystallized salt is soluble in one part of alcohol (95%). When the salt is exposed to the air it loses its alcohol of crystallization and takes up two and a half molecules of water instead.

3. A neutral hydrochloride containing half a molecule of water of crystallization. This salt is obtained by exposing the salt mentioned sub 2) to a temperature of 35° to 40°. At this temperature the salt loses all its alcohol of crystallization and takes up half a molecule of water.

This salt is the most stable of the series taking up moisture much more slowly than either the salt obtained by removing the water of crystallization from the salt sub 1) or the salt obtained by removing the alcohol from the salt sub 2).

4. A hydrochloride containing three molecules of water of crystallization. This salt is obtained by exposing the anhydrous salt obtained either from 1) or 2) to a very damp atmosphere. In an atmosphere saturated with moisture the salt becomes liquid.

The specific rotation of anhydrous quinine hydrochloride was found to be $a_D = -233°$. Journ. Pharm. Chim. XX, 347.

According to C. Erba quinine hydrochloride when recrystallized from alcohol does not contain one and a half molecules of alcohol (see preceeding paragraph) but one molecule alcohol and one molecule water. Journ. Pharm. Chim. XX, 550.

**Ricinine.** Maquenne and Philippe have investigated the constitution of ricinine. The alkaloid was prepared by exhausting the deoleated seeds with hot water, concentrating the liquid to small volume, adding then a mixture of alcohol and chloroform and after

distilling off the solvent recrystallizing the residue from boiling water. One kg. of the seeds yielded about 2 grams of alkaloid.

Ricinine has a very bitter taste, is difficultly soluble in all solvents and crystallizes in thin plates melting at 201°. Its formula was found to be $C_8H_8N_2O_2$.

On saponifying ricinine with potassium hydroxide a molecule of methyl alcohol is split off and ricininic acid is formed.

$$C_8H_8N_2O_2 + H_2O = CH_3.OH + C_7H_6N_2O_2$$

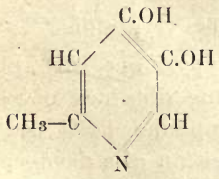
Ricininic acid.

Ricininic acid crystallizes from water in shining needles difficultly soluble in water or alcohol and is decomposed without melting at about 320° (on the bloc Maquenne).

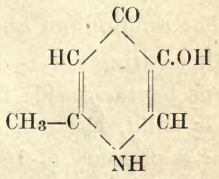
On heating ricininic acid with fuming hydrochloric acid to 150° carbon dioxide and ammonia are liberated and the hydrochloride of a new base is formed

$$C_7H_6N_2O_2 + 2H_2O = CO_2 + NH_3 + C_6H_7NO_2$$

This new base crystallizes in needles containing one molecule of water of crystallization and is almost completely insoluble in ice water. Crystallized it melts at 80°, anhydrous it melts 170°—171°. It is a very weak base, colors ferric chloride red and forms nitro and bromine derivatives. It is supposed to have the constitution of a methyl dioxypyridine or a methyl oxypyridone

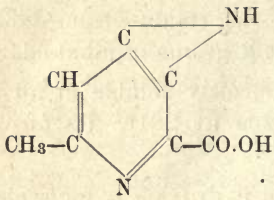



Methyldioxypyridine.

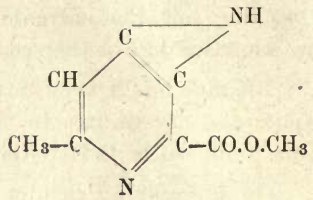



Methyloxypyridone.

Ricininic acid seems to be imino-$\alpha$-picoline carboxylic acid and ricinine the methyl ester of ricininic acid.




Ricininic or imino-
*α*-picoline carboxylic acid.




Ricinine or methyl
ester of ricininic acid.

Bull. Soc. Chim., Paris 1904, 466.

Further work by L. Maquenne and L. Philippe on methyloxypyridone obtained from ricinine (see preceeding paragraph) shows that methyloxypyridone is a very weak base, though it is capable of forming salts with hydrochloric, and phosphoric acids and combining with platinum tetra-chloride. Towards phenolphtalein it behaves even like a monobasic acid. It is neutral towards helianthin and its reaction towards litmus is indefinite. It reduces Fehling's solution in the heat and does not react with hydroxylamine or phenylhydrazine. It forms a mono-, di- and tribromine derivatives which are all easily soluble in alcohol, have a decided acid reaction and are slowly decomposed by hot water but quickly by potassium hydroxide with the elimination of bromine.

On evaporating methyloxypyridone with nitric acid (sp. grav. 1, 2) a nitro derivative, $C_6H_6NO_2(NO_2)$ is formed which crystallizes in yellow needles, has a strong acid reaction forming definite salts with salifiable bases and is very difficultly soluble in hot water. The calcium salt of nitromethyloxypyridone $(C_6H_5N_2O_4)Ca + 5H_2O$ crystallizes in fine needles and is easily soluble in water.

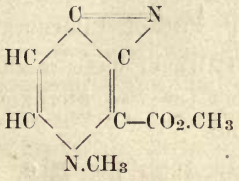
The ammonium and potassium salts are also crystalline.

On heating the hydrochlorfde of methyloxypyridone with phosphorus peutachioride to 160° two substances are obtained of which one is solid, the other liquid. The solid compound boils at 98° under a pressure of 18 mm. and has a composition of a dichlorpyridine, $C_5H_3Cl_2N$. As one methyl group is split off in this reaction the methyl group in methyloxypyridone and hence also in ricinine must be attached to the nitrogen atom, not to carbon as was previously supposed (see preceeding paragraph).

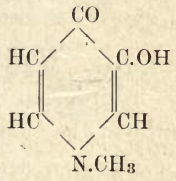
The dichlorpyridine was converted into pyridine by means of

hydriodic acid and red phosphorus and the pyridine identified by converting it into its double salt with mercuric chloride.

From these results the conclusion is drawn that ricinine and its decomposition product methyloxypyridone have the following constitution:



Ricinine.



Methyloxypyridone.

The exact position of the side chains in ricinine is as yet of course unknown.

The acidity of methyloxypyridone which is increased by the introduction of bromine or the nitro group is accounted for by the presence of the CO and OH groups in the molecule.

Compt. Rendus, 139, No. 21, 2ième semestre 840.

**Skimmianine.** J. Honda has isolated a poisonous alkaloid from the leaves of Skimmia Japonica Thunb.

The cut leaves were extracted repeatedly with 96% alcohol at ordinary temperature, the alcohol distilled off and the residue taken up with warm water and filtered. The aqueous liquid was made alkaline and shaken out with chloroform. After distilling off the chloroform the alkaloid was left in yellowish columns melting at 175.5°. The base hardly has any taste but the salts are bitter. It is soluble in alcohol and chloroform but insoluble in water or petroleum ether. The solutions of the alkaloid have a neutral reaction towards litmus. Dilute mineral acids convert the alkaloid into salts only when the acids are in excess and upon concentration of such acid solutions the salts crystallize out in needles. If the excess of acid in solutions of the alkaloid be neutralized with an alkaline carbonate or the alkaloidal salts be treated with alkohol or water the free base separates out.

The alkaloid is precipitated by most alkaloidal reagents. It forms a chloroplatinate and an unstable chloraurate. Concentrated sulphuric acid dissolves the alkaloid with brownish-yellow color. Addi-

tion of potassium chlorate to the sulphuric acid gives a red-brown color. Froede's reagent gives first a green and then a blue color. A solution of potassium permauganate in sulphuric acid gives first a violet and then a brown-yellow colors. Concentrated nitric acid colors skimmianine first yellow, then orange-red.

The formula of skimmianine was found to be, $C_{32}H_{29}N_3O_9$.

Arch. f. exp. Pathol. Pharmak, 52, 83.

**Sparteine.** M. Scholtz and P. Pawlicki have made some experiments in order to determine whether the two nitrogen atoms of sparteine have the same functions or not.

If one nitrogen atom is more basic than the other then alkyl halides ought first to attach themselves to that nitrogen atom which is more basic in preference to the other one. Hence if two different alkylhalides be made to act upon sparteine one after the other we ought to get isomeric but not identical substances when the order in which the alkylhalides are taken is made to vary.

Experiments showed that by taking first methyliodide and then ethyl iodide we really get a substance that is isomeric but not identical with the substance obtained by taking first ethyliodide and then methyliodide. The same was found to be true with methyliodide and the methyl ester of iodo acetic acid or witn benzyliodide and the methyl ester of iodo acetic acid.

On treating sparteine with methyl iodide in presence of methyl alcohol at 100° the hydriodide of sparteine methyl iodide, $C_{15}H_{26}N_2.CH_3I.HI$, was obtained, showing that the methyl alcohol also takes part in the reaction furnishing hydriodic acid by acting upon part of the methyliodide.

By the action of ammonia upon this salt sparteine methyliodide, $C_{15}H_{26}N_2.CH_3I$, was obtained identical with the sparteine methyliodide previously obtained by Bamberger by the action of methyliodide upon sparteine in absence of methyl alcohol.

No separation of free sparteine was noticed in this action of ammonia upon the hydriodide of sparteine methyliodide (compare Bamberger, Ann. Chem. Pharm. 235, 376).

On heating sparteine methyliodide with ethyliodide sparteine methyliodide ethyliodide, $C_{15}H_{26}N_2(CH_3I)(C_2H_5I)$ was obtained. The compound crystallizes in plates melting at 239°.

On reversing the order of the alkyliodides the isomeric compound

was obtained in octohedric crystals melting at 246°. In the same way it was found that the compounds obtained from benzyliodide and methyliodoacetate used in different order differed from each other in crystalline form and melting point. The same was also true of methyliodide and methyliodoacetate.

When sparteine hydriodide is treated with methyliodide the same hydriodide of sparteine methyliodide is obtained which is formed from sparteine and methyliodide in presence of methyl alcohol at 100°. The compound has the formula $C_{15}H_{26}N_2.CH_3I.HI$. As in the compound obtained by the first method the $CH_3I$ group must be linked to the less basic nitrogen atom the same must be true of the compound obtained by the second method. But as Bamberger (loc. cit.) has previously shown that in the cold the action of methyliodide upon sparteine in presence of alcohol consists in the formation of sparteine methyliodide not the hydriodide of the latter, we must assume that at first, i. e., in the cold the $CH_3I$ group attaches itself to the more basic nitrogen atom and that only by heating the mixture to 100° hydriodic acid is formed by the action of the alcohol upon the methyliodide giving the hydriodide of sparteine methyliodide. Hence in the second method when we start with sparteine methyliodide, which must contain tne $CH_3I$ group attached to the more basic nitrogen atom, we ought to get the hydriodide of sparteine methyliodide in which the $CH_3I$ group is again attached to the more basic nitrogen atom. In other words the hydriodides of sparteine methyliodide obtained by the two different methods ought to be only isomeric but not identical with each other. But as they are identical it must be assumed that in one of the two methods there is an internal rearrangement of the nitrogen atoms.

By the action of amyliodide upon sparteine in presence of alcohol the hydriodide of sparteine amyliodide, $C_{15}H_{26}N_2.C_5H_{11}I.HI$, was obtained. In the absence of alcohol either sparteine monoamyliodide or sparteine diamyliodide were obtained according to whether one or two molecules of amyliodide were made to react with one molecule of sparteine.

An addition compound of ortho - xylylene dibromide, $C_{15}H_{26}N_2.C_6H_4(CH_2Br)_2$, was obtained by the action of ortho-xylylene dibromide upon sparteine in chloroformic solution. It crystallizes in needles melting at 273°.

Arch. d. Pharm. 1904, 513.

R. Wackernagel and R. Wolfenstein have investigated the constitution of sparteine. They find that, contrary to the statements of Ahrens, sparteine does not contain a $CH_3—N$ group, does not take up two hydrogen atoms forming a dihydrosparteine and does not form a dioxysparteine when oxidized with hydrogen peroxide. The oxidation product obtained by oxidizing sparteine with hydrogen peroxide must belong to the group of amino oxides containing oxygen doubly linked to nitrogen as in the group $\equiv N=O$. This is shown by the fact that this oxidation product unlike sparteine but like all amino oxides is insoluble in ether and that it is very easily reducible back to sparteine.

The presence of a pyrrol ring in sparteine was shown by the vapors of the decomposition products of the alkaloid reddening pine wood moistened with hydrochloric acid.

From all the investigations of sparteine carried out both by the authors themselves and other investigators the authors draw the following conclusions about the constitution of the alkaloid:

There must be in sparteine a combination of a piperidine and a pyrrol ring.

The alkaloid does not contain unsaturated groups; both nitrogen atoms are tertiary and neither is attached to a methyl group.

There must be at least four ring systems in the alkaloid. This follows from the ratio of carbon to hydrogen in the formula of the base, $C_{15}H_{26}N_2$. As the boiling point of sparteine seems to be too low for a four ringed compound it is very probable that there is in sparteine a combination of two bicyclic rings, possibly two norhydrotropidine rings linked together by a methylene group.

Ber. Dtsch. Chem. Ges. 1904, 3238.

**Strychnine.** D. Martin has made some bromine derivatives of strychnine.

Monobromstrychnine, $C_{21}H_{21}BrN_2O_2$, was made by adding a solution of bromine in strong hydrobromic acid (50%) to a solution of strychnine in dilute hydrobromic acid in presence of sodium acetate till the precipitate at first produced did not soon redissolve and then precipitating the brominated alkaloid with ammonia. The monobromstrychnine melts at 199°, is easily soluble in alcohol and acidulated water but difficultly soluble in chloroform, ether or acetone. It combines with methyliodide and ethyliodide and forms a per-

bromide, $C_{21}H_{21}BrN_2O_2.HBr.Br$ when treated with a solution of bromine in hydrobromic acid.

The perbromide melts at 204° and loses its perbromine when dissolved in organic solvents. It is stable in the dark but resinifies when exposed to the light.

On further brominating the monobromstrychnine a dibromstrystrychnine, $C_{21}H_{20}Br_2N_2O_2$, was obtained. The dibromcompound melts at 130°—131°, forms addition products with methyliodide and ethyliodide and a perpromide, $C_{21}H_{20}Br_2N_2,O_2.HBr.Br$, which loses bromine upon solution in acetone.

A periodide of monoiodostrychnine hydriodide $C_{21}H_{21}IN_2O_2.HI.I$ was obtained by boiling a solution of strychnine in excess of dilute sulphuric acid with iodic acid and then destroying the excess of iodic acid by means of a little hydrobromic acid. The periodide melts at 154°, is insoluble in water or dilute acids and dissolves in acetone with separation of iodine.

A diiodo addition product, $C_{21}H_{22}N_2O_2.I_2$, was made by adding a solution of iodine in hydriodic acid in presence of sodium acetate. It is insoluble in water and loses all its iodine upon solution in acetone.

A monoiodostrychnine, $C_{21}H_{21}IN_2O_2$, was prepared by pouring an acetone solution of monoiodostrychnine hydriodide periodide into dilute ammonia. The compound melts at 188° and is soluble in dilute acids. Bull. Soc. Chim. Paris, 1904, 386.

C. Minunni and F. Ferrulli have investigated some reactions of tetrachlorstrychnine. The tetrachlorstrychnine was prepared by treating a solution of strychnine in glacial acetic acid with chlorine. It differs from strychnine in that it gives an oxime when treated with hydroxylamine showing the presence of a CO group whereas strychnine itself not giving an oxime does not contain such a CO group. In the formation of the tetrachlorstrychnine there seems therefore to be an intramolecular change which probably consists in the transformation of a grouping $\begin{matrix}CH=C.OH\\ \quad\quad\quad\quad\end{matrix}$ into a grouping $\begin{matrix}CH_2-CO\\ \quad\quad\quad\quad\end{matrix}$. The two hydrogen atoms in the last grouping are probably replaced by chlorine in the tetrachlorine derivative.

On passing chlorine into a solution of strychnine in glacial acetic acid the hydrochloride of tetrachlorstrychnine, $C_{21}H_{17}Cl_4N_2O_2.HCl. + 2H_2O$ soon separates out. It is insoluble in all organic solvents

but can be recrystallized from hot glacial acetic acid. The hydrochloride crystallizes in small white crystals containing two molecules of water of crystallization, becomes brown at about 200° but does not melt even at 260°. The water of crystallization could not be estimated because the substance on heating loses hydrochloric acid.

The free tetrachlorstrychnine can be obtained by adding ammonia and much water to a solution of the hydrochloride in alcohol. Its formula is $C_{21}H_{18}Cl_4N_2O_2 + H_2O$. It forms a flocculent precipitate which can be recrystallized from hot alcohol. It is also soluble in acetic ether and warm benzol. It becomes brown at 140° and melts with decomposition at 165°—170°.

A hydrazone of tetrachlorstrychnine, $C_{21}H_{18}Cl_2N_2O(N—NH.C_6H_5)$, was prepared by heating an alcoholic solution of the free base with phenylhydrazine hydrochloride and then adding an alcoholic solution of sodium acetate. The hydrazone forms minute crystals which are easily soluble in hot alcohol and hot benzol but difficultly soluble in ether. It becomes dark when heated but does not melt even up to 260°.

While strychnine itself contains no hydrogen that is replaceable by acid radicals there are two such hydrogen atoms in tetrachlorstrychnine. By heating the tetrachlorstrychnine hydrochloride with acetic anhydride for three hours monoacethyl tetrachlorstrychnine, $C_{21}H_{17}Cl_4N_2O_2.CH_3.CO$, is obtained. It is soluble in acetic ether, benzol or alcohol. It becomes brown at 100° and melts at 180°—197°.

A monobenzoyl derivative, $C_{21}H_{17}Cl_4N_2O_2(C_6H_5.CO)$ was obtained by treating the hydrochloride of tetrachlorstrychnine with benzoylchloride in pyridine solution. The benzoyl compound becomes dark at about 220° but does not melt even up to 260°. It is difficultly soluble in alcohol or ether, but easily soluble in benzol, acetic ether or glacial acetic acid.

If free tetrachlorstrychnine instead of its hydrochloride be taken in the last reaction a benzoyl derivative containing one molecule of water of crystallization, $C_{21}H_{17}Cl_4N_2O_2(C_6H_5.CO) + H_2O$, is formed. This benzoyl compound is soluble in hot alcohol from which it separates out on cooling in light yellow crystals. It becomes soft at 130° and melts at 150°—155°.

If acetyl chloride be made to act upon tetrachlorstrychnine in pyridine solution a diacetyl derivative is formed but there is at the

same time an elimination of one molecule of hydrochloric acid. The diacetyl compound corresponds therefore to formula $C_{21}H_{15}Cl_3N_2O_2(CH_3.CO)_2$. It is soluble in acetic ether, alcohol and ether and melts with decomposition at 185°.

A dinitrotetrachlorstrychnine, $C_{21}H_{16}Cl_4(NO_2)_2N_2O_2$, was obtained by heating the hydrochloride of tetrachlorstrychnine with strong nitric acid and recrystallizing the product from alcohol. It is soluble in acetic acid, ether or alcohol. It becomes brown at 170°, blackens at 200° but does not melt even up to 260°. Tin and hydrochloric acid reduce the dinitro compound to a colorless reduction product.

In preparing tetrachlorstrychnine as described above there are formed besides the tetrachlorstrychnine several other chlorine derivatives of the alkaloid. Of these only a hexachlorstrychnine could be isolated in pure condition. The substance is very difficultly soluble in all organic solvents and does not melt up to 260°.

Gaz. Chim. Ital. 1904, 11, 364.

C. Reichard finds that while brucine gives characteristic reactions with mercury or silver salts (See this Review page 117), no such reactions are given by strychnine.

When a solution of strychnine nitrate and copper nitrate is evaporated to dryness the residue has a deep green colored rim. Stannous chloride changes the color to violet but on drying the green color appears again.

If instead of copper nitrate platinum tetrachloride be used the residue when moistened with sulphuric acid and warmed becomes dark red. Brucine treated in the same way gives a yellow color.

When treated with hydrogen peroxide and sulphuric acid strychnine forms a blue colored liquid with a yellow rim. On standing the whole liquid becomes yellow. The yellow substance present in this liquid is insoluble in ether so that when the liquid is shaken up with ether the latter remains colorless.

On warming a mixture of strychnine, sulphuric acid and titanic acid a blue liquid is obtained in which the strychnine crystals can be seen to assume a dark color. Addition of water or application of heat changes the color to yellow.

Brucine gives the same reaction but the addition of water makes the liquid colorless.

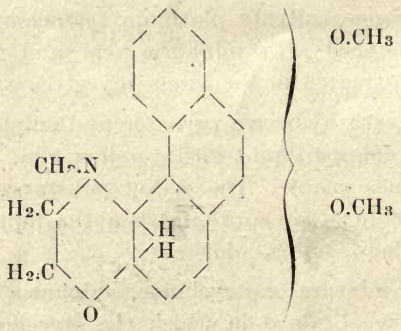
When strychnine is evaporated with some potassium hydroxide to dryness and the residue moistened with a solution of stannous chloride a light blue color is developed.

Brucine does not give this reaction.

With potassium persulphate or ammonium persulphate and hydrochloric acid strychnine gives no reaction whatever in the cold but on warming the liquid assumes a yellow color. Brucine with the same reagents gives a beautiful red color in the cold and the color disappears only upon prolonged standing.

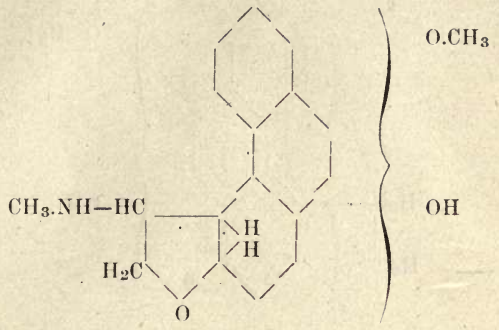
The last reaction can be used to distinguish between strychnine and brucine. Chem. Ztg. 1904, 28, 977.

**Thebenine.** R. Pschorr and C. Massaciu have investigated the constitution of thebenine obtained by the action of aqueous hydrochloric acid upon thebaine or codeinone (See this Review 1904, Prog. Alkal. Chem.). As thebenine contains $CH_2$ less than thebaine and is a secondary base while thebaine is a tertiary base Freund (Ber. Dtsch. Chem. Ges. 3, 1357; 32, 168) explains the conversion of thebaine into thebenine by assuming that in the reaction with hydrochloric acid one $CH_3O$ group of thebaine is saponified, i. e., replaced by an OH group and that the oxazine ring present in thebaine (I) is changed to a furfurane ring in thebenine.




Thebaine.

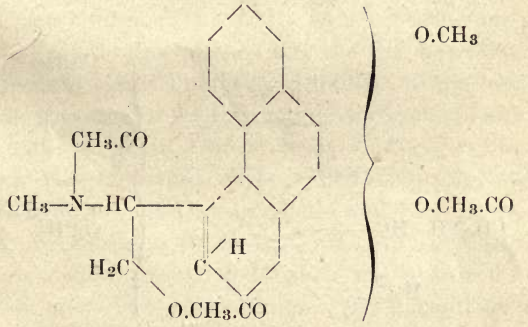
(I)




Thebenine

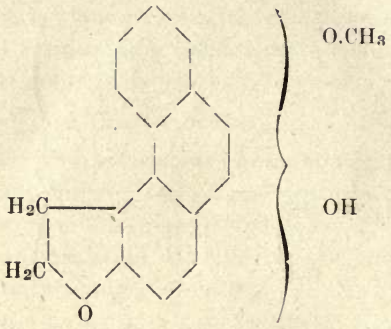
**(II)**

These formulae for thebaine and thebenine satisfactorily explain the formation of triacetyl thebenine (III) by the action




Triacetylthebenine

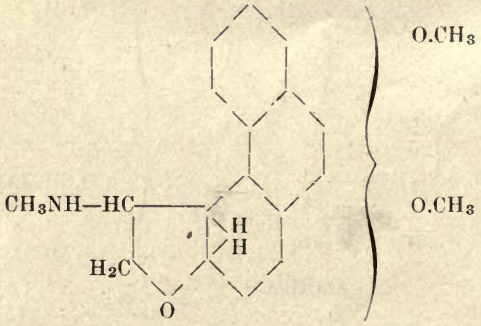
**(III)**




Thebenol

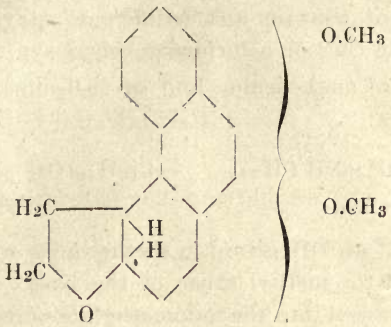
(IV)

of acetic anhydride upon thebenine, the formation of thebenol (IV) from thebenine by means of exhaustive methylation, the formation of methebenine (V), isomeric with thebaine, by the methylation of thebenine and the conversion of this methebenine into methebenol VI) by exhaustive methylation.




Methebenine

(V)




Methebenol

(VI)

According to these formulae there is no free OH group in methebenine (V) and of the three oxygen atoms in thebaine, thebenine, thebenol, methebenine and methebenol one, i. e., the oxygen atom of the oxazine-or the furfurane rings is linked in the same way as in ethers (bridge oxygen).

But a study of the reactions of methebenine by the authors shows conclusively that there must be an OH group in this base. The statement of Freund about the insolubility of methebenine in alkalies is not correct; the base having a weak phenolic character simply requires a large amount (about six molecules) of alkali for solution. From concentrated solutions of methebenine hydrochloride potassium hydroxide precipitates not the free base but its difficultly soluble potassium salt. That the solubility of methebenine in alkali is due to the presence of an OH group and not to any deep change in the molecule, e. g., the opening of an oxygen containing ring, follows from the fact that carbon dioxide precipitates unchanged methebenine from its solution in alkali and that when the alkaline solution of methebenine is treated with hydrochloric or sulphuric acids the same salts are formed which are obtained by the action af these acids upon free methebenine. The formation of a diacetyl and a dibenzoyl derivative by means of cold acetic anhydride or benzoyl chloride also indicates the presence of an OH group in methebenine.

Hence there must be in methebenine an OH group and as the other two oxygen atoms are present in the form of methoxyl groups

methebenine cannot contain an "indifferent" oxygen atom in the form of an oxazine ring or a furfurane ring.

The formulae of methebenine and of thebenine can therefore be resolved as follows:

$C_{16}H_{10}(O.CH_3)_2(OH)(NH.CH_3)$; Methebenine.

$C_{16}H_{10}(OH)_2(O.CH_3)(NH.CH_3)$ Thebenine.

The presence of an OH group in methebenine was also shown by the preparation of the methyl ether of the base. For this purpose the base was converted into the iodomethylate of methyl methebenine and the iodomethylate treated with dimethylsulphate in alkaline solution. Under these conditions the hydrogen of the OH group is replaced by a methyl group and the iodine atom of the $CH_3I$ group is replaced by the anion of the methylsulphuric acid:

$$C_{16}H_{10}(O.CH_3)_2(OH).N(CH_3)_3I + (CH_3)_2SO_4 = C_{16}H_{10}(O.CH_3)_3.N(CH_3)_3.(SO_4.CH_3) + HI.$$

This salt of methyl sulphuric acid can be converted into the corresponding iodide by means of a concentrated solution of potassium iodide:

$$C_{16}H_{10}(O.CH_3)_3N(CH_3)_3.SO_4.CH_3 + KI = C_{16}H_{10}(O.CH_3)_3.N(CH_3)_3I + KCH_3SO_4.$$

When this methylated methebeninemethine methyl iodide is heated with alkali trimethylamine is eliminated and an unsaturated derivative of phenanthrene is formed which contains three methoxyl groups:

$$C_{16}H_{10}(O.CH_3)_3.N)CH_3)_3I = N(CH_3)_3 + HI + C_{14}H_6(O.CH_3)_3.CH=CH_2.$$

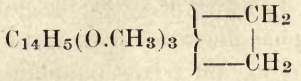
This unsaturated phenanthrene derivative can be easily oxidized to a trimethoxyphenanthrene carhoxylic acid

$$C_{14}H_6(O.CH_3)_3.CH=CH_2 \longrightarrow C_{14}H_6(O.CH_3)_3.CO.OH$$

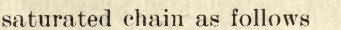
The formation of a trimethoxy derivative of phenanthrene from the methylated methebenine shows that the three oxygen atoms of methebenine must all be in the phenanthrene nucleus.

On the other hand the formation of a monocarboxylic acid from the unsaturated compound shows that the group which in the oxidation is replaced by the carboxyl group is not present in the base in

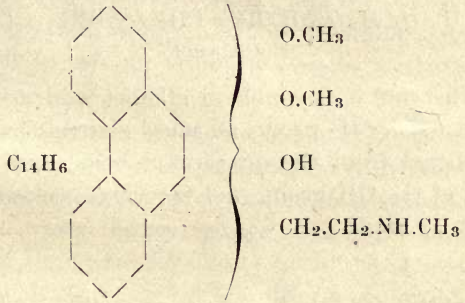
the form of a ring complex (as in this case we ought to get a dicarboxylic acid) e. g. like following



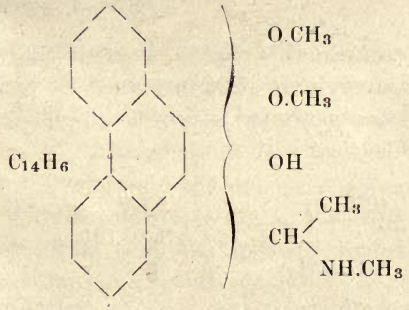
but as an open unsaturated chain as follows



As this unsaturated group is formed only after the splitting off of the amido residue it follows that the nitrogen atom in methebenine must also be situated in this open chain. Hence the formula of methebenine can be resolved into either one of the following expressions:



(VII)



(VIII)

As thebaine was shown by Freund to give oxyethylmethylamine $OH.CH_2.CH_2.NH.CH_3$, among other decomposition products formula (VII) for methebenine would seem to be the more probable one.

According to this phenolic formula for methebenine the compound which is formed by splitting off trimethylamine from the quaternary iodomethylate of methyl methebenine (methebenine methine methyl iodide), i. e., methebenol ought still to contain the OH group present in methebenine and ought therefore to be soluble in alkalies. Besides we ought also to expect that this methebenol would contain the unsaturated group $CH=CH_2$ just like the compound obtained from the methylated methebenine methine methyliodide.

The reaction ought to go according the following scheme:

$$C_{14}H_6(O.CH_3)_2.OH.CH_2.CH_2.N(CH_3)_3I =$$

Methebenine methine methyl iodide

$$C_{14}H_6(O.CH_3)_2.OH.CH=CH_2 + N(CH_3)_3 + HI$$

Methebenol

But as methebenol is insoluble in alkalies and does not contain an unsaturated $CH=CH_2$ group we must assume that in the formation of methebenol from the quaternary base there is an internal rearrangement of the OH group and the vinyl rest with the formation of a furfurane ring:

$$C_{14}H_6(O.CH_3)_2.OH.CH:CH_2 \longrightarrow C_{14}H_6(O.CH_3)_2\begin{cases}CH_2\\ \diagup\diagdown\\ O\end{cases}CH_2$$

Methebenol

**(VI)**

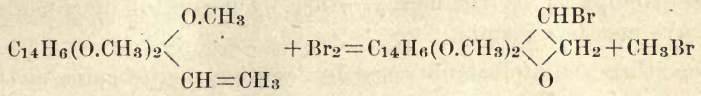
The tendency to form this ring is so great that when the above mentioned trimethoxyvinyl phenanthrene is recrystallized from glacial acetic acid one methoxyl group is saponified and the resulting compound is identical with methebenol:

$$C_{14}H_6(O.CH_3)_2\begin{cases}(CH_3.O)\\ \diagup\diagdown\\ CH=CH_2\end{cases} + H_2O = C_{14}H_6(O.CH_3)_2\begin{cases}CH_2\\ \diagup\diagdown\\ O\end{cases}CH_2 + CH_3.OH.$$

Trimethoxyvinylphenanthrene — Methebenol

**(VI)**

The same formation of the furfurane ring takes place when the trimethoxyvinylphenanthrene is treated with bromine: the resulting compound has the composition of brommethebenol.



Trimethoxyvinylphenanthrene Brommethebenol

The authors have so far not succeeded in establishing the position of the ring forming groups in the phenanthrene complex.

Experimental. The methebenine hydrochloride was prepared by heating a solution of thebaine in methyl alcohol containing hydrochloric acid gas to 100°. It is difficult to obtain the free methebenine in crystalline form, but a crystalline sulphate of the base can be made by adding sulphuric acid to a strong solution of methebenine in alcohol.

If to a strong solution of methebenine hydrochloride (1 in 40) from two to six molecules of normal sodium hydroxide be added the sodium salt of methebenine is precipitated in a gelatinous condition. Upon addition of water the precipitate goes into solution. From a dilute solution of the hydrochloride (1 in 200) the free base is precipitated in amorphous condition upon the addition of one molecule of normal sodium hydroxide. On prolonged standing or slow addition of more sodium hydroxide the base assumes a crystalline form and then goes into solution only after the addition of forty molecules of normal sodium hydroxide.

The freshly precipitated amorphous base requires for complete solution only six to eight molecules normal or tenth normal sodium hydroxide. The sodium salt and the alkaline solution of the base are not stable.

The diacetyl methebenine and the dibenzoylmethebenine were obtained by adding sodium hydroxide to a very dilute solution of methebenine hydrochloride and shaking the solution with acetic anhydride or benzoylchloride respectively.

The methyl ether of methebenine methine methyl iodide (dimethebenine iodomethylate) could not be obtained by the action of methyl-

iodide and sodium alcoholate upon methebenine at 100°. Under these conditions a mixture of methebenol and methebenine iodomethylate is obtained from which both these substances could be isolated and separated from each other by means of ether.

An attempt to get the methyl ether by means of diazomethane also gave negative results.

The ether was at last obtained by treating methebenine methine iodomethylate (which as said above eontains a phenolic OH group and is therefore soluble in alkalies) with dimethyl sulphate in presence of sodium hydroxide and warming the mixture on the water bath. Under these conditions the OH group is methylated and the iodine atom of the $CH_3I$ group is replaced by the group $SO_3.O.CH_3$.

When the methyl ether of methebenine methine methylsulphate obtained in this way is warmed with a concentrated solution of potassium iodide the methyl ether of methebenine methine iodomethylate is formed.

The trimethoxyvinylphenanthrene, $C_{14}H_6(O.CH_3)_3.CH=CH_2$, was obtained by boiling either the iodide or the methylsulphate of the methyl ether of methebenine methine with potassium hydrate for one hour. After the elimination of trimethylamine the liquid on cooling deposits a green mass of trimethoxyvinylphenanthrene which can be recrystallized from alcohol.

The trimethoxyvinylphenanthrene combines with picric acid when both are mixed together in alcoholic solution. The picrate is not very stable and can be recrystallized from alcohol only in presence of some picric acid.

The trimethoxyvinylphenanthrene carboxylic acid, $C_{14}H_6(O.CH_3)_3.CO.OH$, was prepared by oxidizing the trimethoxyvinylphenanthrene in acetone solution with potassium permanganate. After filtering off the $MnO_2$ the liquid was saturated with sodium chloride and shaken out with ether. The yield is about 10 per cent of theory.

The conversion of trimethoxyvinylphenanthrene into methebenol (VI) can be accomplished either by boiling the trimethoxyvinylphenanthrene for a few minutes with glacial acetic acid or by adding to a boiling alcoholic solution of trimethoxyvinylphenanthrene concentrated hydrochloric acid drop by drop till the liquid becomes turbid.

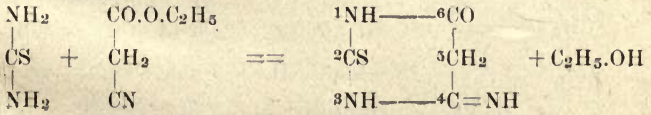
It was shown that methebenol contains only two $CH_3O$ groups, hence one of the $CH_3O$ groups of trimethoxyvinylphenanthrene is eliminated as methyl alcohol in the closing of the furfurane ring.

When trimethoxyvinylphenanthrene is treated with bromine a monobrommethebenol is formed together with some more brominated compound. The monobrommethebenol was also found to contain only two $CH_3O$ groups showing that one of the $CH_3O$ groups of trimethoxyvinylphenanthrene is eliminated as methyl bromide.

Ber. Dtsch. Chem. Ges., 1904, 2780.

**Xanthine Bases.** W. Traube has devised the following syntheses for hypoxanthine and adenine.

Hypoxanthine. On boiling an alcoholic solution of sodium ethylcyano acetate with sulphourea alcohol is split off and a difficultly soluble sodium salt of 4-amino-6, oxy-2, thiopyrimidine separates out from which the free base can be liberated by acetic acid

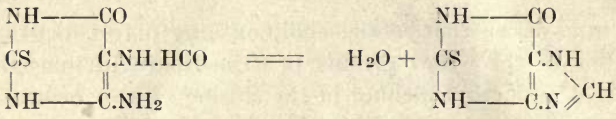


Ethylcyanoacetate 4, amino-6, oxy-2, thiopyrimidine

This pyrimidine compound reacts with nitrous acid giving an isonitroso derivative which by reduction is converted into 4, 5, diamino-6, oxy-2, thiopyrimidine

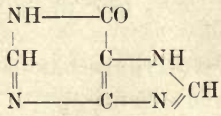
Iso nitroso derivative 4, 5, diamino-6, oxy-2, thiopyrimidine

When the diamino compound is boiled with formic acid a formyl derivative is formed which when heated to 250° loses one molecule water and is converted into 2, thiohypoxanthine



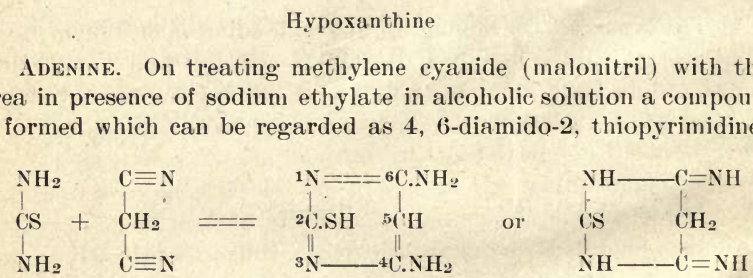
Formyl derivative — 2, Thiohypoxanthine

When this thiohypoxanthine is treated with nitric acid the sulphur is eliminated quantitatively as sulphuric acid and hypoxanthine is formed identical with the natural base

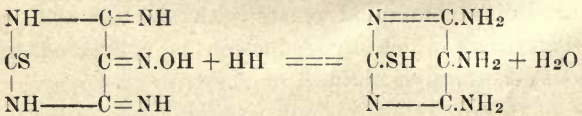


Hypoxanthine

ADENINE. On treating methylene cyanide (malonitril) with thio urea in presence of sodium ethylate in alcoholic solution a compound is formed which can be regarded as 4, 6-diamido-2, thiopyrimidine

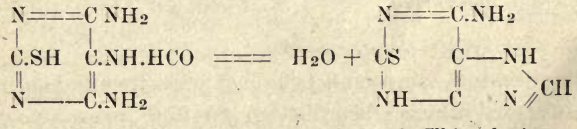


By means of nitrous acid the diamido compound can be converted into an isonitroso derivative which by reduction is converted into 4, 5, 6-triamino-2, thiopyrimidine



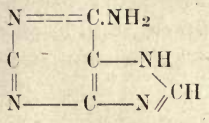
Iso nitroso derivative — 4, 5, 6-Triamino-2, thiopyrimidine

This pyrimidine derivative is changed by formic acid into the corresponding formyl compound which on boiling loses water and is converted into 2, thioadenine



2, Thioadenine

From this thioadenine the sulphur cannot be eliminated by means of nitric acid as is the case of the corresponding hypoxanthine compound, but hydrogen peroxide converts the thioadenine very easily into adenine eliminating the sulphur quantitatively



Adenine

Annal. (Lieb.) 331, 64.

**Yohimbine.** L. Spiegel in collabration with B. Auerbach have investigated the alkaloid yohimbine obtained from Yohimbo bark.

The alkaloid has the formula $C_{22}H_{30}N_2O_4$, but under certain conditions it loses one molecule water forming anhydroyohimbine, $C_{22}H_{28}N_2O_3$. The latter formula underlies the salts of the alkaloid.

On treating yohimbine with alkali the alkaloid is converted into yohimboic acid (noryohimbine).

Yohimboic acid is both a monobasic acid and a mono-acid base and has the formnla $C_{20}H_{26}N_2O_4$.

On treating yohimboic acid with hydrochloric acid gas in the presence of alcohols the hydrochlorides of new compounds are formed in which two hydrogen atoms have been replaced by two alkyl groups and from which, in the case of the lower alcohols, one molecule of water has at the same time been eliminated. Hence the hydrochloride obtained when methyl alcohol is used has the formula $C_{22}H_{28}N_2O_3.HCl$ and is identical with the salt obtained from yohimbine by means of hydrochloric acid.

With isobutyl alcohol there is no elimination of water and the compound obtained has therefore the formula $C_{28}H_{42}N_2O_4.HCl$.

The free base underlying these compounds can be obtained from these hydrochlorides by dissolving them in water and adding ammonia to the solution.

As yohimboic acid is a monobasic acid it ought to take up only one alkyl group in the reaction with hydrochloric acid gas in presence of alcohols.

It is possible (though hardly probable) that one of the alkyl groups attaches itself to the nitrogen atom of the acid. If such be

the case we would have to assume that in the conversion of yohimbine into yohimboic acid both the methyl group present in the carboxyl group and the methyl group attached to the nitrogen atom are eliminated. While experiment has shown that both a methoxyl group and a methylimide group are present in yohimboiic acid it is nevertheless difficult to suppose that in the conversion of yohimbine into yohimboic acid a methyl group attached to nitrogen is so easily split off.

The author hopes to clear up the subject by means of the reaction of diazomethane upon yohimboic acid.

In this reaction there are formed two different substances both of which are converted into yohimbine when treated with hydrochloric acid in presence of methyl alcohol.

Ber. Dtsch. Chem. Ges., 1904.

Northwestern University School of Pharmacy.

# MONOGRAPHS.

1. **Popular German Names.** This popular pamphlet has been revised twice by its author, Dr. Fr. Hoffmann. Price, $0.50.

2. **Reagents and Reactions** known by the names of their authors. Based on the original collection of A. Schneider; revised and enlarged by Dr. Julius Altschul; translated from the German by Dr. Richard Fischer, Asst. Professor of Practical Pharmacy at the University of Wisconsin. Although imperfect in many respects, this compilation has proven a convenient aid in the laboratory and on the desk. A revision is now in progress. As long as any copies of the first edition remain, they can be had for $0.25.

3. **Popular Scandinavian Names.** A compilation of popular Swedish names of drugs and medicines by Harold Bruun, with formulas for the preparation of a number of preparations not generally found in American reference works. This list is also being revised. Copies still on hand can be had for $0.15.

4. **Early Phases in the Development of Pharmaceutical Legislation in Wisconsin.** An account by Edward Kremers of the evolution of the first local pharmacy law in Wisconsin with the documents on which the account is based. Pamphlet, pp. 43. Price $0.50.

5. **Some Cuban Medical Plants.** While collecting plants in Cuba during the year 1895 and 1896, Prof. R. Combs had his attention directed to numerous plants of the island used as domestic remedies. Pamphlet, pp. 20. $0.15.

6. **History of the Art of Distillation and of Distilling Apparatus.** By Oswald Schreiner. Pamphlet, pp. 59, with 65 illustrations. Price $0.35.

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—**Volksbenennungen der brasilianischen Pflanzen und Produkte derselben** in brasilianischer (portugiesischer) und der von der Tupisprache adoptirten Namen. This valuable list has progressed as far as *Sapoquema*.

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1. **Chemical Biography of Morphine.** From 1875 to 1897, with an index of authors and subject index. By H. E. Brown. Pamphlet, pp. 60. $0.40

2. **Santonin.** Bibliography, with abstracts of methods of production etc. From 1830 to 1897. By A. Van Zwaluwenburg. Pamphlet. pp. 11. 0.10

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5. **Bibliography of aromatic waters.** From 1809 to 1900 incl. By W. O. Richtmann. Brochure, pp. 219. 1.00

In addition to the pamphlet form, these bibliographies will be found very convenient for card catalogues which can be kept up to date as indicated by the following fascimile reproduction of such a card.

Gordin and Prescott 1898

Pharm. Archives. 1. p 121.

A volumetric assay of opium. The morphine estimated as periodide, after separation by successive treatment with benzol, acetone and lime water.